



Treatment Action Group

TMC114/r (darunavir/r)

brand name Prezista®

by Rob Camp, 25 May 2006

Who's got the POWER?

Introduction

Darunavir (DRV) is a ritonavir (r) -boosted protease inhibitor that has been studied for use in heavily treatment-experienced patients. In the future, DRV/r will be evaluated for use in less-experienced, treatment-naïve and pediatric populations. The current New Drug Application, and this paper, deal only with Tibotec/Johnson & Johnson (J&J), the sponsor's, current application for accelerated approval for darunavir (formerly known as TMC-114, brand name Prezista®) among heavily treatment-experienced individuals, based on data from the POWER studies.

Development of DRV was spectacularly fast. In fact, before data from efficacy studies were presented publicly anywhere, the sponsor had agreed with FDA to rev up the research program by enrolling more people into an agreed-upon dose, and present it for approval well ahead of schedule. The last time phase IIB data was encouraged by FDA as basis of an approval package was for indinavir in 1996.

Darunavir/r has a standard second-generation PI safety profile. The most commonly reported adverse events across all clinical trials include diarrhea, nausea, fatigue, headache and vomiting. The most common laboratory abnormalities were elevated liver enzymes, triglycerides and lipids.

DRV/r is more bioavailable after a meal, and will be recommended to be administered with food. The dose to be marketed is 600mg DRV + 100mg /r BID.

Twenty-four week data are available from two studies, POWER-1 and -2, in 131 patients, and limited information on 327 others who were enrolled into an open label Phase III cohort (POWER-3) that allows FDA to see data on 458 people with advanced disease (<200 CD4s) at 24 weeks. TAG regrets the lack of a public FDA Antiviral Drug Advisory Committee hearing to discuss the implications of approving a drug with so little public and comparative data. TAG and the undersigned organizations believe that FDA should approve Tibotec's application for accelerated approval of Prezista® brand DRV/r to treat advanced HIV infection in treatment-experienced adults with evidence of HIV-1 replication despite ongoing antiretroviral therapy. This recommendation is based on the follow-up studies in section 2 being commenced and successfully completed in a timely fashion.

This paper will discuss the following issues:

- Executive Summary
- Crucial post-marketing Studies
- Pharmacokinetics, population-specific concerns, Dosing & Drug Interactions
- Safety
- Resistance
- Predictive factors
- Efficacy Studies
- Expanded Access
- Appendix 1 – Pre-clinical data
- Appendix 2 – Interactions tables
- Appendix 3 – Letter to FDA 22 Dec 2004

1. Executive Summary

Ten years of HAART. Development, approval, and marketing of the first three protease inhibitors -- saquinavir (1995), zidovudine (1996), and didanosine (1996) paved the way relatively swiftly for seven subsequent protease inhibitors -- nelfinavir (1997), saquinavir soft-gel capsules (1997, withdrawn 2005), amprenavir (1999), lopinavir/r (2000), atazanavir (2003), fosamprenavir (2003), and tipranavir/r (2005). Currently the most widely used PIs are lopinavir/r and atazanavir, with the ubiquitous ritonavir almost always used in boosting other PIs, rarely on its own. Many of the heavily treatment experienced individuals studied in the sponsor's POWER studies have been through extensive prior PIs and other classes of antiretroviral (ARV) agents. Darunavir is the ninth molecularly distinct PI. What would distinguish it from its predecessors? It can be a healthy addition by showing it can work effectively in a heavily resistance-laden population, having a minimal toxicity burden broken down by gender, race and age, and be reasonably priced.

DRV will be taken as two orange-colored 300 mg tablets plus one 100 mg tablet of ritonavir twice a day, totaling 6 pills per day. It must be taken with food of some kind, which increases absorption by some 30%.

People with hepatitis have barely been part of the program (12% coinfecting with HBV or HCV), and this is one of the blind spots that the sponsor needs to fill in. Even fewer participants in the pivotal studies – just 11% - were women. The data on women submitted for DRV/r is the most paltry ever. 89% men in POWERs-1 and -2 was scandalous, 87% in POWER-3 was insulting. This is a disgrace.

The 24-week virologic efficacy of DRV was looked at head-to-head with a CPI (comparator protease inhibitor). More data on comparative activity versus other combination regimens needs to be generated for safe clinical use. Current data support DRV/r use only in a heavily treatment-experienced population in combination with two nucleoside analogue reverse transcriptase inhibitors (NRTIs). The label should clearly state that DRV has only been studied in this specific setting, with 71% of the people followed on an open label basis.

We are concerned with the lack of publicly available safety data. The people studied may be those same who first got 'crix-belly', who have gone through kidney stones, explosive diarrhea, metabolic changes and whose livers have been working overtime

since their first regimens, 10 years ago. DRV is one more ritonavir-enhanced BID protease inhibitor. The safety profile of DRV/r so far is not alarming, but 25% of patients have reported at least 1 grade 3 or 4 adverse event.

The serious adverse events collected in the tiny EAP have not been categorized or published to help define the risks of DRV use. This should be done immediately. The lack of any significant EAP is unfortunate.

Interaction studies show that most other PIs are contra-indicated, except possibly ATV, although its C_{min} is raised by some 87%. Darunavir plus atazanavir plus 100 mg ritonavir results in an increase in RTV levels by just under 60% as well (Sekar 2006). ATV should be used only on an as-needed basis. For IDV use, please see section 3, Other ARVs.

DRV/r is effective in the presence of primary mutations (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V, L90M). Based on available clinical data, DRV/r is active against strains of HIV-1 that are resistant to commercially available protease inhibitors (having been studied in people with a median of 3 primary PI mutations).

The speed of development deserves recognition from the community. This is probably due in part to the FDA's pangs of guilt over having approved a quite toxic, partially effective salvage drug -- tipranavir -- in June 2005, and thus wanting to help those most in need as fast as possible.

While we admire the flexibility of all parties concerned, the lack of an Antiviral Advisory Committee (AVAC) hearing precisely when so little is known about DRV/r, is worrisome. HIV community groups strongly support public hearings whenever a new molecular entity (NME) application goes to the FDA for approval. People with HIV, activists and care providers all benefit from the open discussion that is part of the AVAC hearing process. They are a valuable opportunity for participation and learning.

We hope that FDA takes a more flexible, pro-active role with respect to advisory committees and their hearings, while continuing to use them whenever needed. We also remind FDA that prompt on-line publication of its interpretation of the dataset is vital, including documentation of safety, statistical, subgroup, and efficacy concerns, and a clear list of required post-marketing studies.

Although pricing doesn't fall directly under FDA's regulatory umbrella, we direct your attention to a proposal by the Fair Pricing Coalition that calls for corporate responsibility in pricing this and other new ARVs (Fair Pricing Coalition 2006). Two posters have been presented showing DRV's 'value' in today's market, at scientific congresses, an interesting approach to price non-neutrality, but not necessarily convincing from an objective point of view, since the research sponsor is the same as the product manufacturer. Named patient programs in Europe (similar to compassionate use programs in the US) are being charged approximately twice what Kaletra costs -- just a squeak under the price of Aptivus/r (Johnson 2006). At EACS in Dublin, Tibotec/J&J presented a model that purported to suggest that a person taking DRV/r would have half the death rate (hazard ratio 47-55%) of someone on a comparator PI (Montaner 2005). Such models depend on the robustness of the data which go into them, and since there are no survival data on DRV/r they should be regarded as speculative at best, promotional at worst.

The US and European HIV treatment community has been fortunate to have worked closely with Tibotec over the past 3 years. While the process has been far from perfect, it has allowed a sense of collaboration (witness the DUET studies) that we seldom achieve with industry, and it is a model worth repeating.

In summary, DRV/r has advantages -- including an acceptable resistance profile and reasonable tolerability -- and disadvantages -- including lack of long-term and population-specific data, and a potentially high price. Used properly, it may be a helpful addition to the current pharmacopeia. Before full approval is granted, the community believes the following studies must be done:

2. Crucial Post-Marketing Studies

FDA should require the following studies to be successfully completed; in addition we support legislation to strengthen FDA's ability to mandate completion of such studies, and to sanction sponsors who fail to meet their commitments.

Dosing. Is the chosen dose the optimum dose? In advanced patients, all four dosing strategies were efficacious.

Populations. Should this drug be approved in women? Are there enough data? The sponsors opted for faster approval rather than look for ways to be more inclusive (by specifying target numbers, for example). Is a warning sufficient at this point until the GRACE study (70% women) results come in? Is there a need to state on the label that potential gender differences are likely to have been missed in women? Are liver challenged people being given a fair shake? Further studies are needed to characterize DRV/r's effects in liver-impaired people, and under what circumstances DRV/r may be contraindicated. We understand that a liver-impairment study is now enrolling in 'mild-to-moderate' impairment. The FDA approved labeling for darunavir should prominently state the lack of significant data from women and coinfecting persons.

Other patient populations. The sponsors are doing a head-to-head study with Kaletra with an 800mg/100mg r QD dose in naïves, called the ARTEMIS study. Why is the dose here different than the 600mg/100 mg BID dose (the highest dose studied in the POWER studies, and the dose submitted to FDA for approval)? There is also a post-first line trial, in a one-PI-failure scenario, called TITAN, where 50% of patients will be women. It's not clear what the optimal dose is either for first line or subsequent use.

Drug-drug interaction/PK studies. Interaction studies need to be done with antiarrhythmics, anticoagulants, anticonvulsants, calcium channel blockers, antibacterials, immunosuppressants, itraconazole, amphetamine and amphetamine derivatives, hormonal contraceptives, methadone, buprenorphine, rifampin, rifapentine, fibrates, ribavirin, fosamprenavir, ergot derivatives, midazolam, triazolam and pegylated interferon. Data from the etravirine interaction study needs to be made public now. The two may well be often used together. The label must indicate whether PK data are available in women and coinfecting persons.

Long-Term Safety.

Resistance studies. Which resistance profiles predict response or lack thereof to DRV/r? Who ought to wait for a second active agent (e.g., etravirine, or an integrase

inhibitor) in certain cases of resistance? What are the signature mutations after the failure of DRV/r? Larger, more comprehensive, longer-term, real-life studies could help here.

Pediatrics. No data have been generated for pediatric use. There is no formulation yet. The sponsor promises a trial in ages 6 and up with a 75 mg tab. We expect that 24-week results are available within a year.

3. Pharmacokinetics, Specific Populations, Dosing & Drug Interactions

A year from now, when DRV would otherwise be under consideration for accelerated approval, many of the outstanding questions above and below would probably have been answered, ahead of the majority of drug interaction studies done by most companies. We are encouraged that the sponsor has been able to investigate most of the drugs in the 'by approval' list in Appendix 1. They should be published quickly. For the 'by 6 months' list, patients need to have the outstanding answers within 2006.

Gender, race, hepatic, renal impairment

Ten percent higher drug levels have been observed in women (Sekar 2006). The caveat is that the number of women is so low in the POWER studies that definitive conclusions can't be drawn about dosing or safety. Would you be confident using this in women? The label should specify that data in women is lacking. The currently-enrolling GRACE study will enroll 70% women and also attempt to redress underenrollment of racial and ethnic minorities. In all 3 POWER studies, just 53 women have taken this drug at the to-be-approved dose – 12% of the total. The sponsors are targeting a 50% enrolment of women in their TITAN study. Postponing studies in half the human race until after approval is simply unacceptable in 2006. How might one find women? Where are they hidden? Make a target number. The CRO won't get paid until they reach that number (by heightening trust and motivation, reaching out to local women's groups, orchestrating a PR campaign, bringing on additional sites).

As for race, no differences were seen, but again, numbers were small (>75% Caucasian in the POWERS). No differences were seen in HBV or HCV coinfecting people, although again numbers were small (12% of total) and there was no stratification. A study in hepatically impaired subjects has started recruitment. Details are lacking. As for those with renal impairment, an early AME (absorption, metabolism, excretion) study showed additional studies will not be needed (Shurtleff 2004).

Exposure to DRV/r increases by 30% with food, which will be a recommendation. Tibotec looked at 4 types of breakfast – croissant with coffee, a protein-rich nutritional drink, a high fat breakfast, and a standard breakfast – and all of them showed a similar increase over no food (Hoetelmans 2004, Sekar 2005). Even though defining the food may be culturally helpful, any type of breakfast looks like it boosts DRV/r. Refreshingly, they looked at 12 men and 12 women in this HIV- study.

Other ARVs

In older formulations of both drugs, TMC114/r lowered levels of TMC125 (etravirine) by 35% (no effect of 125 was seen on 114.) They have not done a PK study with the final formulations, but a small and short study by Marta Boffito in London presented at CROI (12 weeks) and BHIVA (16 weeks) showed a similar (~30%) decrease in 11 people in a salvage situation. No dose adjustment is deemed needed (Boffito 2006, Jackson 2006).

Even though there is a large Phase III program of DRV/r + ETV underway (the DUET studies), the drug interactions between the two have not been characterized in HIV+ people. Boffitto did a quick and simple trial to get an idea of the safety and efficacy of this combination at the Chelsea and Westminster Hospital. The investigators looked at the pharmacokinetics, resistance, safety, and efficacy of DRV/r 600/100 mg BID and ETV 200 mg BID plus NRTIs with or without T-20 (ENV). Of 11 subjects, 10 completed the study; median (range) baseline characteristics included age 43 (38 to 56) years; CD4 - 75 (3 to 490) copies/mm³; viral load 4.6 log₁₀ (3.9 to 5.5); number of mutations (IAS, October 2005) for protease inhibitors, -primary 4 (0 to 5), -associated 11 (2 to 13), for NRTI 7 (2 to 9), and for NNRTI 2 (0 to 6). 6/10 people had prior exposure to TPV/r and to T-20; 2 used T-20 for the first time (Boffito 2006).

Day 28	darunavir	etravirine	darunavir hr	etravirine hr
AUC ₀₋₁₂ mean (SD)	72,321ng.h /mL (21687)	4921ng.h/ mL (2982)	123,336 ng.h/mL	11236 ng.h/mL (3210)
C _{max} mean (SD)	9109ng/ml (2482)	569ng/ml (381)	9000ng/mL *	1263 ng/mL (345)
C _{0h} mean (SD)	5175ng/ml (2011)	340 ng/mL (213)	3539ng/mL	625 ng/mL (227)

hr = historical reference

Compared to historical references, these reflect unchanged exposure to DRV and a > 30% reduced exposure to TMC125 (in HIV- studies, a 33-37% change had been seen) (Vingerhoets 2006). So, despite a reduced exposure to 125, at week 6, all subjects had achieved at least a 2 log₁₀ decrease in viral load with a median of -2.55; 5/10 and 8/10 had viral load < 40 and 400 copies/mL, respectively. DRV/r and ETV work together, and this small study is a proof of concept (albeit retroactive) for the larger DUET studies, the registrational program for ETV now underway.

With atazanavir, the C_{min} rises some 87% and the two should be used together only if needed (C_{max} and AUC are unchanged). With IDV, maculopapular rash is more evident – some 20% of people discontinue due to it. Also, more numbness around the lips, nausea and headache are reported with IDV. Saquinavir, tipranavir/r and lopinavir/r are not recommended (Interactions chart, App. 2). The sponsors have presented a lack of interaction with either T20 or efavirenz (Sekar 2005). TDF exposure is increased some 22% (Hoetelmans 2004). Phase II trials have shown that there were no safety or tolerability concerns with co-administration of FTC and DRV. With NNRTIs, EFV lowers DRV exposure by 13%, and DRV raises levels of EFV by 21% (Sekar 2006). There is no NVP data. There is no significant interaction between DRV and T20, and they can be safely coadministered (Sekar 2006). With the two remaining CCR5 antagonists, CDAs are in place with Pfizer and Schering to discuss healthy volunteer studies for DRV/r. A CDA is in place with Merck to study the interaction with MK-0518, and co-enrollment of appropriate patients in the TMC114 EAP and the Merck MK-0518 studies, is allowed.

With PA 457, the maturation inhibitor, an interaction is deemed unlikely and there are no plans to study that. Same for TNX-355, a monoclonal antibody, no interaction is expected.

Other common drugs

A DRV study is ongoing with hormonal contraceptives. The anticipated outcome is that estrogen levels are lowered as seen with other boosted PIs, so other contraceptive methods will be recommended. With methadone, a DRV study is ongoing. Anticipated outcome: drug lowers methadone levels, while the opposite is expected with buprenorphine (dose will need to be lowered). Rifabutin (100 mg every other day) and sildenafil (1/4 dose) will need to be modified. Echinacea can be combined with DRV/r (Interaction chart, App. 2).

With lorazepam, temazepam, etc, no studies are planned. Their concomitant use is allowed, and no effect is expected. Darunavir lowers SSRIs sertraline and paroxetine by 40%. Even so, their concomitant use is allowed. There are no interactions with PPIs or H2 antagonists, they are allowed. No reaction is expected with either glitazones or metformin, and they are allowed. There was no effect of 20mg omeprazole on DRV (40 mg was not looked at), nor was there any effect of 150 mg BID ranitidine on DRV. No dose adjustment needed for clarithromycin, depending on individual renal function. No dose adjustment needed for ranitidine. Both DRV and ketoconazole levels are raised when administered together (Interactions chart, App. 2).

Pravastatin is not recommended, atorvastatin at 10 mg (Hoetelmans 2004).

Many drugs are unknown or still only theoretically allowed, see full chart in Appendix 2. TAG laments FDA not being able to convince sponsors to do more, earlier. Please see the letter sent in December 2004 re: timelines of when the most common drugs should be concurrently studied (Appendix 3). That much being said, the sponsor has done more than the less-than-minimum normally seen by approval and we hope to see even greater advances with their next compounds, and that they may be looked at as a leader in the field to be emulated (and hopefully surpassed!) by other companies.

4. Safety and side effects

Side effects were less than benign. Again, in this highly treatment-experienced population, rash, lipids, cardiac, liver, and glucose measurements were all seen to increase, similar to most other PIs. This population, more vulnerable to side effects due to longer treatment history and longer history of having HIV, is not getting a kind or gentle salvage therapy.

Forty-two percent of the HIV- participants in one early study reported headache, 21% diarrhea, 13% pruritis, and 8% vomiting (Peeters 2004).

The following safety data was provided by all patients treated with the recommended dose of DRV/r 600/100 mg (POWER 1, 2 and 3) (Pozniak 2006). Diarrhea (16%), nausea (12%), nasopharyngitis (12%) and headache (11%) were the most common side effects. Headache, relatively common in POWER-1 and -2, was less prevalent in POWER-3. Twenty-nine percent of both DRV/r and CPI patients reported ≥ 1 grade 3 or 4 AE, regardless of causality. Grade 3 or 4 AEs occurring with an incidence of $\geq 2\%$ are displayed at the end of this section. The incidence of serious adverse events (SAEs) in

the DRV/r groups was 13.1%. Grade 3 and 4 liver-related events were reported in 5% of DRV patients and 7% of those on control PIs.

There was no dose relationship between DRV dose and the frequency and/or severity of AEs.

Safety within HBV or HCV coinfecting people was similar between arms (with or without DRV/r). One grade 4 clinical hepatotoxicity was seen in an early study of 600/100 BID. It resolved upon stopping all drugs.

In POWER-2, the DRV/r arms had double the SAE profile compared to the control arm. Much work went into providing health-related quality of life surveys in these studies. The resulting data needs to be presented.

Darunavir is a sulfonamide (Koh 2003), but to date, no potential for cross sensitivity between sulfonamides and DRV has been identified in people taking DRV. The incidence of rash-related AEs was 7% with DRV/r; all except one rash event was of grade 1 or 2 severity. ABC was not allowed as first-time exposure in POWER-3.

There were 3 deaths in POWER-1, 6 in POWER-2, 6 in POWER-3 (3% total). None of these deaths was considered related to treatment with DRV/r by the investigator or the relevant DSMBs.

The nine deaths reported in POWERS-1 and -2 were due to

- methicillin-resistant *Staphylococcus aureus* (MRSA),
- AIDS-related lymphoma,
- adenocarcinoma,
- pseudomembranous colitis,
- acute myeloid leukemia,
- multi-system failure,
- illicit drug overdose,
- progressive multifocal leukoencephalopathy, and
- failing chemotherapy treatment for acute leukemia.

In addition, a tenth fatal case was reported in the control group, with a probable cause of death being nosocomial infection. The majority of all deaths occurred in people with less than 50 CD4.

No clinically relevant treatment-related changes over time in laboratory parameters were noted. Incidence of grade 3 or 4 lab abnormalities was similar in the DRV/r groups and the control group. No apparent relationship between DRV/r dose and incidence of observed lab abnormalities was noted with the exception of triglyceride elevations of grade 3 or 4, which were more frequently observed in the DRV/r 600/100 mg BID dose group (the final dose chosen) (Berger 2005). When evaluating all patients initiated with the DRV/r 600/100 mg dose, the incidence of grade 3 or 4 triglyceride elevations was 9%. Total cholesterol was also higher with DRV/r than with any control PI.

25% of patients reported ≥ 1 grade 3 or 4 AE in POWER-3, very similar to POWER-1. Grade 3 or 4 AEs occurring with an incidence of $\geq 2\%$ are displayed at the end of this section.

Grade 3/4 triglyceride, cholesterol, ALT and AST elevations occurred in 6%, 4%, 2% and 1% of patients, respectively. Mean changes in lipid laboratory parameters between baseline and Week 24 were small, with mean changes (SD) from baseline of -0.34 (3.20), 0.43 (1.37) and 0.42 mmol/L (0.89) recorded for triglycerides, total cholesterol and LDL, respectively. The incidence of grade 3 and 4 lipid-related events was 4% for DRV/r patients and 3% for those on control PIs.

There was a pronounced decrease in triglycerides at Week 24 for patients who received LPV/r during screening then received DRV/r during the study period relative to those who did not receive LPV/r. No obvious differences in changes from baseline in other lipid parameters were observed between these two subgroups of patients.

ACTG grade 3 or 4 AEs or laboratory abnormalities in P-3 reported with an incidence of $\geq 2\%$ in DRV/r-treated patients:

AE	n	(%) Patients (n=327)
Mean exposure (weeks)	24	
Any grade 3 or 4 AE	83	(25)
AE by preferred term*		
Diarrhea	5	(2)
Laboratory parameter (worst grade)		
General biochemistry		
Amylase	21	(7)
Lipase	10	(3)
General haematology		
Partial thromboplastin time	10	(3)
White blood cell count	24	(7)
Haematology differential counts		
Lymphocytes	16	(5)
Neutrophils	18	(6)
Total absolute neutrophil count	16	(5)
Lipid and glucose		
Total cholesterol	13	(4)
Triglycerides	18	(6)
Liver function		
Alanine amino transferase	8	(2)
Gamma glutamyl transferase	10	(3)

*Excluding laboratory abnormalities reported as AEs

Discontinuations due to AEs were 4% for DRV/r and 5% for CPI patients. Overall, 11% of DRV/r patients discontinued (3% due to virological failure). Serious AEs occurred in 13% of patients but no individual SAE occurred in $>1\%$ patients (Pozniak 2006).

Tolerability in a late stage drug is hard to judge – discontinuations or lack thereof may not be a reliable marker of tolerability if there is nowhere to go, treatment-wise. People in the CPI arms could have gotten off early ('failed') in order to go to the DRV/r arm as soon as they could.

Better systems are urgently needed to monitor chronic and long-term side effects after drugs are approved. The current adverse events reporting system is voluntary and may miss substantial toxicity. A network of "sentinel practices" to report unusual symptoms might be a viable enhancement to the current inadequate MedWatch system. The need for a better system to detect and track side effects (such as the emergence of lipodystrophy syndrome after the approval of the first protease inhibitors) has long been a major concern for the community.

5. Resistance

Baseline viral load and baseline phenotype (primary PI mutations) were helpful in predicting the efficacy of DRV/r, although it did retain efficacy at high (>100,000 copies/mL) baseline VL (Peeters 2005). There was an unclear correlation between number of primary PI mutations at baseline and virological response, although it was somewhat effective even in the presence of 4 or more primary PI mutations.

At CROI 06, resistance data on 131 people was presented. Virologic response seems consistently favorable until there are 10 or more PI-associated mutations at baseline (IAS-USA March 2005). This sub-analysis of the POWER-1 and -2 trials showed that viral load reduction for darunavir/r was significantly greater than for any CPI ($p < 0.0001$), sensitive or resistant (de Meyer 2006).

Pheno/genotypes of plasma viruses and site-directed mutants were determined by Virco. At week 24, efficacy was analyzed by baseline genotype and sensitivity to the CPI using phenotypic cut-offs of 10 for LPV/r, 2.5 for SQV, 2.5 for APV, and 2.4 for ATV; HIV RNA data were analyzed by the ITT NC=F method.

Wk 24 of POWER-1 and -2 pooled data

	darunavir/r		
Group	(600/100 mg BID)	Sensitive CPI	Resistant CPI
<i>n</i>	112	31	81
HIV RNA log ₁₀ (viral load) change	-1.90	-0.76	-0.37
% ≥1 log ₁₀ reduction	71	36	14
% <50 copies/mL	47	25	9

Virologic response seems consistently favorable until there are 10 or more PI-associated mutations at baseline (IAS-USA March 2005). Moreover, the presence at baseline of mutations V11I, V32I, L33F, I47V, I50V, I54L or M, G73S, L76V, I84V and/or L89V was associated with a diminished response (<50 copies/mL) in patients not using ENF.

Logically, with a background of a substantial number of PI-resistance mutations, particular additional mutations may be associated with reduced DRV susceptibility. Particularly, PI mutations at V32I and I54L, and less so at L33F, I54L and L89V developed upon failure (either rebounding or never suppressed).

31% of patients had previously used TPV. Baseline resistance to TPV (using a clinical cut-off of 3.0) was associated with an increase in DRV FC; therefore, less positive results.

For example, for those achieving a ≥ 1 logHIV RNA reduction

	POWER (-1 and -2)	RESIST	
	Darunavir/r	CPI/r	TPV/R CPI/r
ENF-naïve (%)	88	31	64 30
ENF not used (%)	65	17	40 19
HIV RNA reduction	-1.90	-0.49	-0.8 -0.25
CD4 count rise	+98	+17	+34 +4

Not a lot of data on the mutations selected at DRV failure has been presented. On a handful of people, the mutations not present at baseline that developed in >10% of people were the V32F, I54L, L33F, I84V, I47V and the M46I (in that order). One interesting in vitro analysis presented at CROI 06 looked at the relative contribution to resistance of certain mutations (fitness) (de Meyer 2006). In the background of M46I, I84V and L90M, the addition of V77I was negligible, the addition of I54L or L33F added 6 fold levels of resistance. The I47V (on top of M46I and I50V) reduced susceptibility by 10 fold, while adding K20I and M36I was negligible. The L10I caused a 2-fold reduction in susceptibility.

5A. Predictive Factors influencing treatment response

Inhibitory quotients (IQ) (the ratio between steady state DRV trough concentration and baseline DRV EC₅₀) were shown to be related to efficacy (virologic and response parameters). In POWERS-1 and -2, the IQ was the strongest predictor of virologic response at week 24, with the relationship primarily driven by baseline darunavir fold change (FC). IQ values of darunavir were generally high (mean values >200), increasing with dose. There was no apparent relationship between darunavir PK and safety (Katlama 2005, Wilkin 2005). Although the investigators say that this data implies the dosing choice of 600/100 is justified, it tells me that a high IQ is helpful although not necessary for a sustained response to darunavir/r. Efficacy was strongly influenced by baseline DRV fold change, baseline viral load and use of sensitive drugs in the optimized background regimen (OBR), less so by PK.

In POWER-3 as well, in a multivariate analysis, baseline phenotypic DRV FC was also the strongest predictor of response. A higher proportion of patients achieved any virologic efficacy parameter with a baseline DRV FC ≤ 10 (50%) compared with patients with FC >10 (13%). The majority of patients had DRV FC values below or equal to 10 (Molina 2006).

There was poor correlation between number of primary PI mutations at baseline and virological response.

Higher rates of virological suppression (HIV RNA <50 copies/mL) were achieved with other active agents:

- 29%, 48% and 41% of patients with 0, 1 or ≥ 2 NRTIs in their OBR, respectively,
- the virologic response: -1.27 logs with 0 agents, -1.67 with 1 agent, -2.15 with 2 agents,
- 45%, 27% and 42% of patients using ENF for the first time (naïve), using ENF non-naïvely and not using ENF, respectively.

At BHIVA, an analysis was presented pooling all subjects treated with 600mg bid in Power 1, 2 and 3, it was seen that the more active agents one had, the stronger the response – -1.27 logs with 0 agents, -1.67 with 1 agent, -2.15 with 2 agents (Pozniak 2006).

In this pooled analysis, a total of 24% of patients had previously used TPV. Baseline resistance to TPV (using a clinical cut-off of 3.0) was associated with an increase in DRV FC; the observed change in VL of -1.38 log₁₀ copies/mL for TPV-resistant patients was lower than the overall value of -1.74 log₁₀ copies/mL for all patients who initiated treatment with DRV/r 600/100mg bid.

POWER-3:

Baseline characteristics	n	Response rate n (%)
TMC114 FC		
≤10	170	85 (50)
10–40	33	3 (9)
>40	35	6 (17)
CD4 count (cells/mm ³)		
<50	74	16 (22)
50–100	37	10 (27)
100–200	49	27 (55)
≥200	82	44 (54)
Primary PI mutations		
1	17	6 (35)
2	32	19 (59)
3 or more	194	71 (37)
Susceptible NRTI in the OBR		
0	86	25 (29)
1	91	44 (48)
2 or more	58	24 (41)
Use of ENF		

Previously ENF-naïve	53	24 (45)
ENF re-used	49	13 (27)
ENF not used	144	61 (42)
Prior use of TPV		
Yes	81	25 (31)
No	165	73 (44)

Investigators saw that those with an FC >40 did much worse (failing much more frequently). Those people composed less than 10% of the total subjects studied, and may have done better being in an OLSS of both TMC drugs (de Meyer 2005, 2006). And for all the people in POWER-1 and -2 who were in the suboptimal dosing arms and did not go into POWER-3, were they offered (esp. if they were failing) the option of rolling over into an OLSS of both drugs, ie the best care, even if it is outside the trial?

6. Efficacy studies

POWERs-1 and -2 were five-arm dose finding studies in 588 people in Europe, Australia and the Americas. POWER-3 is an ad hoc rollover of people on the suboptimal (lower dose) arms to 600/100 BID (n=24) and newbies (n=303), designed and implemented to beef up the numbers for approval. The total number of POWER people is 458.

Background regimens were OBT (2 NRTIs with or without T20; no NNRTIs) vs best-selected PI (people had had a median of 4 PI-experience) plus 2 NRTIs with or without T20.

42% of people reached <50 copies/mL at 24 weeks in all 3 POWERs (Pozniak 2006). Although the data looks decent, it is limited. Open label POWER-3 has efficacy at 24 weeks. Not everyone has safety data at 24 weeks. Some of the 131 people in POWER-1 and -2 will reach 144 weeks in late summer 2006. The DUET trial (enrolling now) of DRV/r vs DRV/r + ETR will give us more info, but not for at least a year.

Higher rates of virological suppression were achieved by those who had ≥1 active ARV in their OBR.

Phase II, IIB, IIB/III

The POWER-1 and -2 studies are randomized, controlled, multi-phase studies to evaluate dose-response after 24 weeks in triple class-experienced subjects with at least 1 primary PI mutation and viral load >1000 copies/mL. Everyone was optimized to a NRTI background /r or a CPI/r (investigator-selected comparator protease inhibitor) of choice. Darunavir PK parameters, area under the curve and trough concentration were analyzed in 468 people (all arms of POWERs 1 and 2). At week 24, efficacy was analyzed by baseline genotype and sensitivity to the CPI using phenotypic cut-offs; analysis was by viral load (ITT, non-completer = failure). POWER-1 happened in the US and Argentina, -2 in Europe, Canada, Australia and Brazil (Katlama 2005, Wilkin 2006, Molina 2006).

POWER-1 and -2 had a screening period of 6 weeks originally followed by a 96-week treatment period, and a 4-week follow-up period. There were 4 different DRV treatment

arms (400/100 mg DRV/r QD, 800/100 mg DRV/r QD, 400/100 mg DRV/r BID, and 600/100 mg DRV/r BID) and a control group (CPI). This did not happen. Long before 96 weeks, long before 24 weeks, the sponsor and FDA took the decision to define the best dose and run with it – at the week 24 interim analysis, when approximately 300 subjects had reached 16 or 24 weeks of treatment in each trial.

In public, 497 subjects were included in the interim analysis (397 in all DRV/r arms combined, 100 in control) in POWER-1 and -2. Of these 497 subjects, 329 people reached the 24-week visit or discontinued earlier. All subjects who were treated for at least 4 weeks at that time point were included in the analysis.

Baseline characteristics

In the interim analysis of POWER-1 and -2, the median duration of DRV treatment ranged from 20.1 to 24.0 weeks for the different treatment groups. The average baseline \log_{10} viral load was 4.57 copies/mL and the median CD4+ cell count was 141 (172 for POWER-1, 79 for POWER-2). The mean time since start with ARV therapy was 9.4 years. The mean duration of treatment with PIs, NNRTIs and NRTIs was 5.5, 2.1 and 8.3 years, respectively. The fusion inhibitor T-20 had been previously used by 16% of people with a mean treatment duration of approximately 1 year. Overall, the percentage of subjects with 0, 1, or, ≥ 2 sensitive ARVs in the optimized background regimen (OBR) were 17%, 35% and 48%, respectively. Based on the phenotypic profile (Antivirogram), 66% of the subjects' virus was resistant to all commercially available PIs. Approximately 61% of the subjects had 3 or more primary PI mutations at baseline, according to the IAS-USA list, October 2003.

POWER-1, Rio 2005

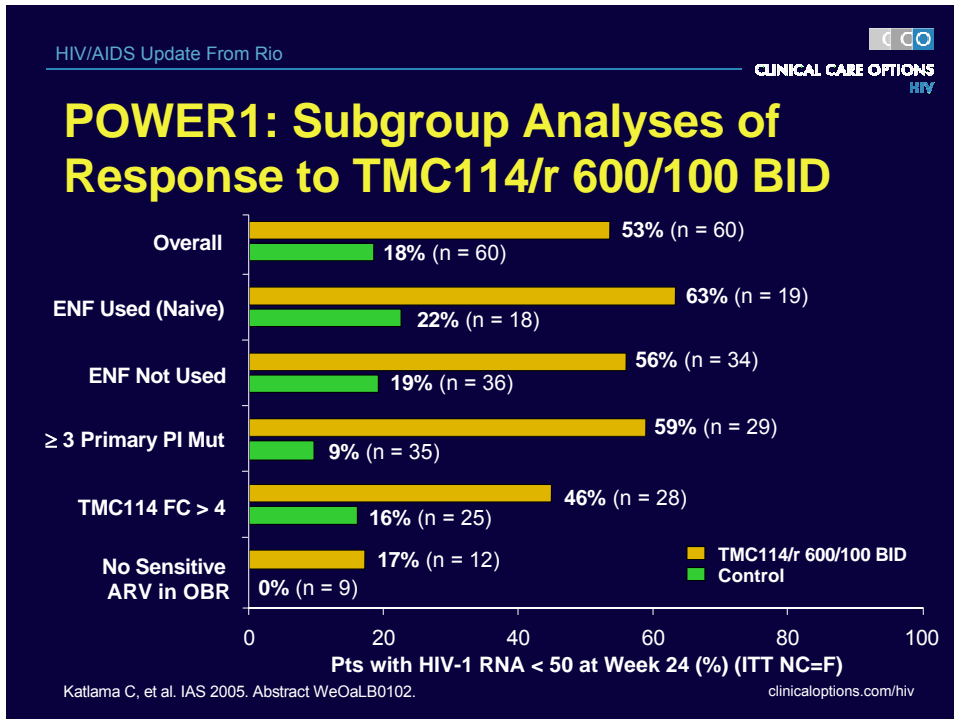
Christine Katlama (H Salpetrie, F) presented the 24-week data on POWER-1 at the IAS Pathogenesis meeting in Rio in July 2005. This trial was also presented in two posters there, by safety and efficacy. DRV/r data was pooled from all the dosing arms vs the CPI/r arm.

The results of the Week 24 interim analysis demonstrated that DRV/r treatment exhibited a superior antiretroviral effect when compared with CPI.

At Week 24, DRV/r treatment resulted as follows relative to CPI:

- 53% vs 18% achieved plasma VL <50 copies/mL (ITT-TLOVR),
- higher proportion of subjects with > 1.0 \log_{10} drop in viral load (77 vs 25%),
- higher proportion of virologic responders (plasma viral load < 50 copies/mL), although that seemed to peak at wk 12,
- higher mean increase in absolute CD4+ cell count (+124 at 24 weeks).

The difference in dosage response was minimal. All doses seemed to start to lose power by weeks 8 – 12, although all arms were still responding virologically at around 70% at 24 weeks. The one analysis where the 600/100 arm did significantly better was the change in CD4 count, where a +124 rise was registered (vs +70 – +75 for the other arms).



Although Katlama only presented all DRV/r vs CPI (no breakdown by dose), I add some TORO data (the T20 pivotals) and some RESIST data (the TPV/R pivotals) to give an idea of the relative power of 114/r.

	114/r	Control	TORO	Resist
CD4s	204	233	90	155
Yrs of tx	9	9	10	11
+T20	45%	43%	62%	45%
viral failure	4%	54%	54%	60%
vl change	-1.8 log	-0.6 log	-1.55 log	-0.88 log
CD4s	+85	+20	+90	+36

T20 +DRV/r got a 67% positive response (>1 log drop) vs 54% on TPV/R. In this population, the least advanced of the POWERS, 79% of the participants had at least 1 active NRTI in the backbone.

They chose to move forward with the 600/100 BID dose, although the differences in virologic responses were indistinguishable. They chose the 600/100 because it should offer the power and durability and forgiveness factor (fingers crossed) desired.

POWER-2, ICAAC 2005

Demographics	DRV/r/CPI	
	DRV/r	CPI
n	225	53
Male (%)	92	89
Mean age (years)	45	46

<u>Disease characteristics</u>		
Mean duration of infection (years)	12.9	14.1
Mean VL (log ₁₀ copies/mL)	4.7	4.6
Median CD4 count (cells/mm ³)	99	113
<u>Treatment history (mean)</u>		
ARVs used (n)	11	11
PIs used (n)	4	4
PI therapy (years)	5	5
Median lopinavir fold-change	78	83
Median primary PI mutations* (n)	3	3
Median PI-resistance-associated mutations* (n)	8	8

Tim Wilkin of Cornell-Weill presented POWER-2 at ICAAC, where the population was more advanced than in -1, and efficacy results were not quite as spectacular, possibly speaking to the need of needing at least two active agents. In the 400 mg QD arm, plasma VL <50 copies/mL was only 18%; in the 800 mg QD, plasma VL <50 copies/mL reached 20%; and interestingly, 400 mg BID did almost as well as the 600 mg arm, at 36% <50.

	POWER 1	POWER 1	POWER 2	POWER 2	POWER 1 & 2	POWER 1 & 2
	600/100m g bid	CPI(s)	600/100m g bid	CPI(s)	600/100mg bid	CPI(s)
People with ≥1 log ₁₀ plasma VL reduction (%)	77	25	62	14	71	21
People with HIV RNA <50 copies/mL (%)	53	18	39	7	48	14
Mean VL reduction (log ₁₀ copies/mL)	2.0	0.63	1.7	0.3	1.9	0.49
Mean CD4 increase (cells/mm ³)	124	20	59	12	98	17

For DRV/r 600/100mg bid vs CPI(s):

- $\geq 1.0 \log_{10}$ VL reduction: 62% vs 14% of patients
- VL <50 copies/mL: 39% vs 7% of patients
- mean VL reduction: 1.7 vs 0.3 \log_{10} copies/mL
- mean CD4 increase: +61 vs +12 cells/mm³ (LOCF)

The efficacy results of the interim analysis of these two POWER trials showed that all selected dosages of DRV/r exhibited an antiretroviral response (a statistically significant difference in the \log_{10} viral load change versus baseline at Week 24 (NC = F) of all dosages vs the control group was obtained). Plasma DRV trough concentrations were above the target (550 ng/mL) defined for PI resistant virus in the majority of the subjects in all dose groups. In addition, all doses of DRV/r showed an AE profile comparable to, although not better than, the control group.

POWER 3, BHIVA

POWER 3 is a non-randomised, open-label cohort of DRV/r conducted to assess the long-term efficacy and safety of DRV/r 600/100mg BID in treatment-experienced patients, presented by JM Molina at BHIVA 06. The primary efficacy endpoint was the proportion of patients with $\geq 1\log_{10}$ reduction in HIV RNA by Week 24 (ITT, TLOVR).

In total, 327 patients were enrolled; 246 reached Week 24 by 24 September 2005 and were reported on to FDA as part of the accelerated package. Median baseline characteristics were between those of POWER 1 and 2: viral load was 4.6 \log_{10} copies/mL and CD4 count was 116 cells/mm³. As before, participants needed to have at least 1 PI mutation from the IAS-USA 2004 list of primary PI mutations: D30N, L33I/F, M46I/L, G48V, I50V/L, V82A/F/L/T/S, I84A/C/V, L90M12. 20% of patients had sensitivity to another licensed PI at screening (Antivirogram®) excluding tipranavir (TPV), which was not available at the time of study recruitment.

Of the 327 patients, 303 were newly recruited and had not participated in any prior TMC114 study, and 24 others had 'rolled over' from the control arm of previous TMC114 studies following significant virological failure (<0.5 \log_{10} reduction in plasma HIV RNA from baseline at or beyond Week 12) treated with 600/100 from the start.

The primary efficacy endpoint of $\geq 1 \log_{10}$ reduction at HIV RNA was observed in 65% (160/246) of patients. Reductions in HIV RNA levels to <400 copies/mL and <50 copies/mL were seen in 57% (n=141) and 40% (n=98) of patients, respectively. The mean reduction in HIV RNA from baseline to Week 24 was $-1.65 \log_{10}$ (standard deviation [SD]=1.36). CD4 counts at Week 20 rose by a mean of 80 cells/mm³ (SD=99), which is similar to the result from the Week 24 efficacy analysis of DRV/r patients in the POWER 1 and 2 trials, where CD4 counts rose by 122 and 61 cells/mm³.

HIV RNA <50 copies/mL and a reduction in HIVRNA of $\geq 1\log_{10}$ copies/mL were achieved by 40% and 65% of patients, respectively. In all 3 POWERS, 52%, 38% and 40% of people got below 50 at 24 weeks.

Clinical and laboratory AEs were graded by severity and relation to study drug (by trial investigators).

Parameter	POWER 1 (n=65)	POWER 2 (n=66)	POWER 3 (n=327)
Demographics			
Gender (% female)	14.5	6	12.5
Mean age (yrs)	42	46	44
Race (% Cauc'n)	89	73	75
Disease characteristics % CDC C	38	35	55
Mean duration HIV infection (years)	11.1	12.9	12.8
Mean HIV RNA (log ₁₀ copies/mL) (SD)	4.59 (0.69)	4.62 (0.68)	4.62 (0.76)
Median CD4 (cells/mm ³)(range)	176 (6–708)	115 (3–776)	115 (20)
Previous ARV exp Mean duration (months) (SD) NRTI	107 (38)	93 (55)	112 (40)
NNRTI	29 (20)	28 (28)	27 (20)
PI	67 (26)	62 (32)	69 (33)
Prior PI use (TPV) (%)	3	5	31
(LPV/r) (%)	80	82	88
Prior use of enfuvirtide (%)	11	27	30
Median IAS-USA primary PI mutations (range)*	2 (0 – 5)	3 (1 – 5)	3 (0 – 6)
Median PI resistance-associated mutations (range)*	8 (0 – 12)	8 (1 – 12)	9 (0 – 13)
≥1sensitive PI (%)	39	33	20
≥1sensitive NRTI in OBR (%)	77	67	61

*2005

7. Expanded Access

Expanded access was somewhat of a farce. The sponsor touted an availability of 24,000 slots (50 countries) they were 'ready to serve' in an EAP. The real number is probably closer to 1% of that. Possibly, they couldn't afford to offer it to anyone based on need (those who especially might need it with TMC125) because every person mattered as a trial participant. Their FDA date trumped everything, unless you are Julio Montaner. In

the first 3 months of 2005, only 130 US people enrolled. Either there are a lot less people in salvage or there were too many hoops, including site access and cost.

The author would like to thank Heidi Nass for her insights.

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AIDS Action Baltimore, Inc
AIDS Treatment Data Network, NY NY
ATAC's Drug Development Committee
The Center for AIDS Information & Advocacy, Houston TX
The Community HIV/AIDS Mobilization Project (CHAMP)
CorrectHelp, Los Angeles CA
The International Foundation for Alternative Research in AIDS, Portland, OR
Test Positive Aware Network, Chicago IL
Salvagetherapies.org

Appendix 1: Pre-Clinical Data through to final formulation

(Compiled by author based on referenced data)

DRV is a novel non-peptidic PI containing 3(*r*),3a(*S*),6a(*r*)-*bis*-tetrahydrofuranylurethane (*bis*-THF) and a sulfonamide isostere (Tie 2004). DRV EC₅₀ (50% effective concentration in cell based assays) = 4.6 nM (2.5 ng/mL), an EC₉₀ (90% effective concentration in cell based assays) = 10 nM (5.5 ng/mL) and a CC₅₀ (50% cytostatic concentration in cell-based assays) > 100 μM for wild-type HIV (strain LAI), which makes it a potent and selective HIV inhibitor, with a selectivity index (SI) > 20000 (Surleraux 2005). In vitro, the molecule showed no or a slight decrease in potency against highly PI-cross-resistant clinical isolates (de Béthune 2001).

The agent showed limited toxicity in single and multiple dose studies and absence of mutagenic or clastogenic potential in a complete battery of genetic toxicology tests. No observed adverse effect levels (NOAELs) were derived from 6-month repeated dose studies in rats and dogs. In the rat study the NOAEL was determined at 20 mg/kg and in dogs the NOAEL was determined at 120 mg/kg. The target organ in rats is the hematopoietic system. In dogs no clear target organ has been identified yet (Arasteh 2005).

Phase I trials / healthy volunteers / DRV alone

In humans, DRV was rapidly absorbed when administered as an oral solution. After the absorption phase, an initial rapid distribution/elimination phase was followed by a slower elimination phase. In vitro studies have demonstrated that DRV is mainly metabolized by cytochrome P450 (CYP) 3A4. The highest single DRV dose administered alone and as oral solution (PEG) to humans was 3200 mg. At this dose level, the mean C_{max} (maximum plasma concentration) and AUC_{last} (area under the curve) were 14407 ng/mL and 51835 ng.h/mL, respectively. C_{max} was reached within 0.5-1.5 hours after intake. The terminal elimination half-life was in the order of 10 hours. Due to the high frequency of diarrhea, dose escalation was discontinued at 3200 mg. The incidence of diarrhea was likely related to the increasing amounts of the solvent polyethylene glycol (PEG) 400 of the oral solution with increasing doses (Hoetelmans 2003).

Phase I / healthy volunteers / co-administered with ritonavir

After repeated dosing of 1200 mg TID as oral solution, relatively low minimum plasma concentrations (C_{min}) (142 ng/mL) and high maximum concentrations (C_{max}) were observed (8040 ng/mL). Therefore, the effect of low doses of RTV on the pharmacokinetics of DRV was investigated. After repeated dosing, the mean C_{min} , C_{max} and $C_{ss,av}$ (average steady-state plasma concentration, calculated by AUC/t at steady-state) at Day 14 were 1278, 5453, and 2460 ng/mL for 1200 mg DRV /200 mg RTV once daily, respectively. Compared to DRV administered alone, higher values for C_{min} of DRV could be obtained at lower total daily doses of DRV, and with a smaller C_{max}/C_{min} ratio during the dosing interval (Sekar 2006).

After repeated dosing of DRV alone, the most frequently reported AEs in healthy volunteers were maculopapular rash, starting 8-10 days after treatment, and diarrhea, mostly starting after 2-3 days of treatment (Hoetelmans 2004).

From oral solution to tablet

The majority of the Phase I studies and the Phase IIa studies were performed with a PEG400-containing oral solution. For long-term treatment, a solid formulation of DRV was developed. A direct compression tablet was selected for use in clinical studies. Results from a food interaction study demonstrated a decrease in exposure to DRV by 30% if taken under fasted conditions. Under fed conditions (with 100 mg /r), the relative bioavailability of a single 400-mg dose of DRV administered as a tablet was comparable to the oral solution in healthy volunteers. The mean DRV C_{max} and AUC_{last} were 3701 ng/mL and 45608 ng.h/mL for the oral solution, and 3614 ng/mL and 43938 ng.h/mL for the tablet (Hoetelmans 2004).

A trial investigating the repeated dose pharmacokinetics and dose proportionality of DRV administered as a tablet with /r in healthy volunteers was done. 5 dose regimens were tested (DRV/r 400/100 QD, 800/100 QD, 1200/100 QD, 400/100 BID, and 800/100 BID). The result showed that DRV trough concentrations increased dose proportionally for all regimens. For the 2 doses with the same total daily dose studied (800 mg), the daily exposure was similar ($C_{ss,av}$ 2546 ng/mL for the 400/100 mg BID and 2793 for the 800/100 mg QD dose groups).

DRV is formulated as 400 mg tablets (for 800 mg total in naives) or 300 mg tablets (600 mg total in experienced people) for oral administration. The tablet is composed of DRV ethanolate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate and Opadry®Orange (Lefebvre 2005). (Ritonavir (r) is formulated as a capsule containing 100 mg r and the inactive ingredients butylated hydroxytoluene, ethanol, gelatin, iron oxide, oleic acid, polyoxyl 35 castor oil and titanium dioxide.) (package insert 2006)

Random ramblings

There has been an increasing impetus to assess the burden of HIV using patient-reported outcomes such as health-related quality of life (HRQL) instruments, particularly in the clinical trial setting. This multidimensional construct defines the subjective understanding of the impact a disease and its treatment have on physical, psychological, and social well-being and functioning. As more effective therapeutic options for HIV infection are being developed, interest in health-related quality of life outcomes is further increasing. We look forward to seeing the results of the many HRQL surveys that were done.

The community worked hard with Tibotec to keep a subjective investigator-centered analysis of alcohol / drug use from being an exclusion criteria. The current language is more person-friendly, but data regarding drug or alcohol users has not been made public yet.

All HIV-infected subjects should be advised to take the necessary precautions to reduce the risk of transmitting HIV. Although the goal is worthy, why preach safe sex and abstinence in a treatment trial?

The following description applies for lack or loss of treatment response: Plasma HIV-1 RNA greater than 50 copies/mL at or beyond Week 24 that is confirmed by 2 consecutive measurements. Confirmation can be obtained by performing an unscheduled visit. Are clinical trials going too fast? Saying that 2 consecutive tests above 50 = failure, is that realistic? What is a person with no other treatment options (which is purportedly the case in these Phase III trials) to do?

Appendix 2: Established and Theoretic Drug Interactions With TMC114
(Tibotec data, June 2005)

Drug Class	Interaction Effect	Clinical Comment ^a
Antiretrovirals		
• PIs		
- Ritonavir (RTV)	↑ TMC114 (increased plasma concentrations).	Allowed. Only TMC114 in combination with low-dose RTV as pharmacokinetic enhancer (100 mg b.i.d.) is allowed.
- Lopinavir (LPV)/RTV	↓ TMC114 (relative bioavailability decreased by 53%). ↓↑ LPV (relative bioavailability of LPV was decreased by 19% with TMC114 alone and increased by 37% with TMC114/RTV).	Disallowed. It is not recommended to combine LPV/RTV and TMC114 (with or without RTV).
- Saquinavir (SQV)/RTV	↓ TMC114 (exposure decreased by 26%). SQV: no significant changes.	Disallowed. It is not recommended to combine SQV and TMC114/RTV.

- Atazanavir	TMC114: not influenced. ↑ Atazanavir; only increase in C_{min} (50%).	Allowed. Atazanavir at a dosage of 300 mg q.d. can be coadministered with a TMC114/RTV b.i.d. regimen.
- Indinavir	↑ TMC114 (increased plasma concentrations; AUC_{12h} increased by 24%). ↑ Indinavir (AUC_{12h} increased by 23%)	Allowed. Dosing recommendations: When used in combination with TMC114/RTV, dose adjustment of indinavir to 600 mg b.i.d. (instead of 800 mg b.i.d.) may be warranted in case of intolerance.
● NRTIs		
- Tenofovir disoproxil fumarate (TDF)	↑ tenofovir (systemic exposure increased by 22%). TMC114: not influenced.	Allowed. Increase of systemic exposure of tenofovir is not clinically relevant. TMC114/RTV and TDF can be co-administered without dose adjustments.
- Didanosine	Data on interaction with TMC114/RTV currently not available.	Allowed. Didanosine should be administered on an empty stomach. Therefore, didanosine should be administered 1 hour before or 2 hours after TMC114/RTV (administered with food).
- Zidovudine, zalcitabine, emtricitabine, stavudine, lamivudine and abacavir	Data on interaction with TMC114/RTV currently not available.	Allowed. These NRTIs are primarily excreted renally and have a different elimination pathway than TMC114/RTV. Therefore, no drug interactions are expected.
● NNRTIs		
- Efavirenz (EFV)	↓ TMC114 (C_{min} : 31% decreased; exposure is decreased by 13%). ↑ EFV (exposure is increased by 21%).	Allowed. Based on the interaction and on the results with Phase IIb trials, the combination of TMC114/RTV and EFV can be used without dose adjustments.
- Nevirapine (NVP)	No relevant changes in exposure of TMC114 or NVP.	Allowed. The combination of TMC114/RTV and NVP can be used without dose adjustments.
- Delavirdine (DLV)	No interaction data available	Disallowed. It is not recommended to combine DLV and TMC114 at this time.
● Vaccines		
- Experimental Vaccines		Disallowed.

- Approved Vaccines		Allowed. Should be given at least 4 weeks before a viral load measurement.
• Other medicinal products		
• Antiarrhythmics		
- Bepridil, flecainide, propafenone, systemic lidocaine, quinidine, mexilitine, disopyramide and amiodarone	Data on interaction with TMC114/RTV currently not available.	Disallowed. Concentrations of bepridil, flecainide, propafenone, lidocaine, quinidine, mexilitine, disopyramide and amiodarone may be increased when co-administered with TMC114/RTV.
• Anticoagulants		
- Warfarin	Data on interaction with TMC114/RTV currently not available.	Disallowed. Warfarin concentrations may be affected when co-administered with TMC114/RTV.
• Anticonvulsants		
- Phenobarbital, carbamazepine and phenytoin	Data on interaction with TMC114/RTV currently not available.	Disallowed. Phenobarbital, carbamazepine and phenytoin are inducers of CYP450 enzymes. Co-administration of phenobarbital, carbamazepine or phenytoin with TMC114/RTV may cause significant decreases in TMC114 plasma concentrations, which may result in loss of therapeutic effect.
• Calcium channel blockers e.g., felodipine, nifedipine, nicardipine	Data on interaction with TMC114/RTV currently not available.	Disallowed. Calcium channel blockers (e.g., felodipine, nifedipine, nicardipine) may have their plasma concentrations increased when TMC114/RTV is administered concomitantly.
• Antibacterials		
- Telithromycin	Data on interaction with TMC114/RTV currently not available.	Disallowed. Telithromycin concentrations may be affected when co-administered with TMC114/RTV.
- Clarithromycin	Data on interaction with TMC114/RTV currently not available.	No dose adjustment is necessary for subjects with normal renal function. For subjects with renal impairment, the following dosage adjustments should be considered: Creatinine

		<p>Clearance (CLcr) 30-60 mL/min - the dose of clarithromycin should be reduced by 50%. CLcr less than 30 mL/min - the dose of clarithromycin should be decreased by 75%.</p> <p>It is advised not to exceed a total daily dose of 1000 mg of clarithromycin and to monitor the subject carefully</p>
- Dexamethasone	Data on interaction with TMC114/RTV currently not available.	Disallowed (only topical formulations allowed). Dexamethasone induces CYP3A4 and can therefore decrease TMC114 plasma concentrations, which may result in loss of therapeutic effect.
• H2-receptor antagonists and proton pump inhibitors		
- Omeprazole or ranitidine	No effects.	Allowed. No dose adjustments are warranted.
• <u>Immunosuppressants</u>		
- Cyclosporin, rapamycin, tacrolimus, sirolimus	Data on interaction with TMC114/RTV currently not available.	Disallowed. Plasma concentrations of cyclosporine, rapamycin, tacrolimus or sirolimus may be increased when co-administered with TMC114/RTV.
- Ketoconazole and itraconazole	Data on interaction with TMC114/RTV currently not available.	Allowed (Only up to 200 mg/day dose). Ketoconazole and itraconazole are potent inhibitors as well as substrates of CYP3A4. Concomitant systemic use of ketoconazole or itraconazole and TMC114/RTV may increase plasma concentrations of TMC114. Simultaneously, plasma concentrations of ketoconazole and itraconazole may be increased by TMC114 and RTV

<p>• Lipid-lowering agents and HMG-CoA reductase inhibitors</p>		
<p>- Pravastatin</p>	<p>↑ pravastatin (exposure increased with approximately 80% but only due to increases in a subset of subjects). TMC114/RTV: not affected.</p>	<p>Disallowed.</p>
<p>- Lovastatin and simvastatin</p>	<p>Data on interaction with TMC114/RTV currently not available.</p>	<p>Disallowed. Lovastatin and simvastatin, are highly dependent on CYP3A4 metabolism and are therefore expected to have markedly increased plasma concentrations when co-administered with TMC114/RTV. Increased concentrations of statins may cause myopathy, including rhabdomyolysis. Do not co-administer lovastatin or simvastatin with TMC114/RTV.</p>
<p>- Atorvastatin</p>	<p>↓ atorvastatin (15% lower plasma exposure after a single dose of 10 mg atorvastatin in the presence of TMC/RTV compared to a single dose of 40 mg atorvastatin alone).</p>	<p>Allowed. Dosing recommendations: Recommended to start with 10 mg atorvastatin q.d. A gradual dose increase may be tailored to clinical response. Careful monitoring for signs and symptoms of muscle weakness or myopathy, including rhabdomyolysis, is recommended.</p>
<p>- Rosuvastatin</p>	<p>Data on interaction with TMC114/RTV currently not available.</p>	<p>Allowed. Rosuvastatin is not metabolized by CYP3A4 in a clinically significant extent; TMC114 is primarily a CYP3A4 inhibitor. Therefore, a metabolic interaction between TMC114 and rosuvastatin is unlikely. Dosing recommendations: Recommended to start with 5 or 10 mg rosuvastatin q.d. A gradual dose increase may be tailored to clinical response.</p>
<p>- Methadone</p>	<p>Data on interaction with TMC114/RTV currently not</p>	<p>Allowed. When methadone is co-administered with</p>

	available.	TMC114/RTV, methadone levels may be decreased, as RTV is known to induce the metabolism of methadone, leading to a decrease in its plasma concentrations. Dosing recommendations: Currently not established. Monitor for signs and symptoms of methadone withdrawal; some subjects may need an increase in the methadone dose.
- Amphetamines and amphetamine derivatives	Data on interaction with TMC114/RTV currently not available.	Disallowed. Co-administration of amphetamines or amphetamine derivatives and TMC114/RTV may lead to significant increases in the exposure to amphetamine (derivatives).
- Astemizole, terfenadine	Data on interaction with TMC114/RTV currently not available.	Disallowed. Potential for increased astemizole and terfenadine effects (e.g., cardiac arrhythmias) due to inhibition of CYP3A4 by TMC114/RTV.
- Oral contraceptives	Data on interaction with TMC114/RTV currently not available.	Allowed. Plasma concentrations of ethinylestradiol may be decreased by induction of its metabolism by RTV. Dose recommendations currently not established. Alternative or additional contraceptive measures are to be used when estrogen-based oral contraceptives are co-administered with TMC114/RTV.
- PDE5 inhibitors	↑ sildenafil (plasma exposure is the same after a single dose of 100 mg sildenafil alone compared to a single dose of 25 mg sildenafil in the presence of TMC114/RTV).	Allowed. The PDE5 inhibitors sildenafil, vardenafil and tadalafil are highly dependent on CYP3A4 for their metabolism. Dosing recommendations: If concomitant use of

		<p>TMC114/RTV and sildenafil, vardenafil or tadalafil is indicated, sildenafil at a single dose not exceeding 25 mg in 48 hours is recommended, as this provides similar exposure as 100 mg sildenafil alone.</p> <p>Alternatively, vardenafil (no more than a single 2.5 mg dose in 72 hours) or tadalafil (no more than a single 10 mg dose in 72 hours) is recommended.</p>
- Rifabutin	Data on interaction with TMC114/RTV currently not available.	<p>Allowed. Rifabutin is an inducer and substrate of CYP450 enzymes. Concomitant use of rifabutin and TMC114 in the presence of RTV is expected to lead to an increase in rifabutin plasma concentrations, and a decrease in TMC114 plasma concentrations.</p> <p>Dosing recommendations: When indicated, it is recommended to administer rifabutin in a dosage of 150 mg once every other day when combined with TMC114/RTV.</p>

- <u>Rifampin, Rifapentine</u>	Data on interaction with TMC114/RTV currently not available.	Disallowed. Rifampin is a potent inducer of CYP450 metabolism. TMC114 and RTV should not be used in combination with rifampin, as this may cause significant decreases in TMC114 plasma concentrations. This may result in loss of therapeutic effect.
- St John's wort, Echinacea	Data on interaction with TMC114/RTV currently not available.	Disallowed. TMC114 and RTV should not be used concomitantly with products containing St. John's wort (<i>Hypericum perforatum</i>) because co-administration may cause significant decreases in TMC114 plasma concentrations. This may result in loss of therapeutic effect.
- Cisapride, Pimozide	Data on interaction with TMC114/RTV currently not available.	Disallowed. Inhibition of CYP450 3A4 by TMC114/RTV. Potential for increased cisapride and pimozide effects (e.g., cardiac arrhythmias).
- Ergot derivatives (dihydroergotamine, ergonovine, ergometrine, ergotamine, methylergonovine)	Data on interaction with TMC114/RTV currently not available.	Disallowed. Inhibition of CYP450 3A4 by TMC114/RTV.
- Midazolam, triazolam	Data on interaction with TMC114/RTV currently not available.	Disallowed. Inhibition of CYP450 3A4 by TMC114/RTV. Potential for increased midazolam and triazolam effects (e.g., increased sedation, confusion, respiratory depression).
- Meperidine (pethidine)	Data on interaction with TMC114/RTV currently not available.	Disallowed. Potential for increased normeperidine effects. Induction of CYP450 1A2 by RTV;

		possible inhibition of p-glycoprotein by TMC114/RTV reducing first-pass metabolism of meperidine.
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^a Allowed/disallowed concomitantly with TMC114/RTV.

Appendix 3: Letter to FDA 22 Dec 2004

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Dear Dr Birnkrant,

I am writing to follow up on the productive meeting with the CDER staff and ATAC's Drug Development Committee (DDC) in November 2003. Many things were discussed during this meeting: (please see Bob Huff's article in *Treatment Issues* vol. 17 no. 11 at www.qmhc.org/health/treatment/ti/ti1711.html#3, that reviews specifically

- PK data
- Drug-drug interaction studies
- 'Real life' study populations
- Post-marketing research
- and Long-term side effects (a la sentinel cohorts)).

I am writing solely as a member of the Treatment Action Group to help you think about the first three points - what data needs to be seen with new drugs before approval decisions are made on upcoming drugs.

This letter will focus on pharmacokinetic (PK) issues as they apply to specific populations and drug-drug interaction studies (1), and on further outlining changes we are requesting regarding required or desirable pharmacokinetic and drug-drug interaction data which should be available from sponsors of investigational new drugs (INDs) for treatment of HIV disease and associated complications, either at the time the new drug application (NDA) is submitted, or as part of the suite of required post-marketing studies.

As discussed a year ago, the community is suggesting that certain data be routinely included in every approval package and be required -- or strongly encouraged -- by the FDA of sponsors. In some cases, e.g., accelerated approval, the FDA may have more leverage than in others. However, we encourage the FDA to think creatively about strategies for obtaining and requiring the capture of data necessary to better guide clinical care for people living with HIV. Can approval be deterred until the data submitted?

The studies most needed that would help in better defining the toxicity and safety of new drugs, are:

By approval:

- All currently approved ARVs (including AZT, ddI, d4T, 3TC, ABC, efavirenz, nevirapine, tenofovir, indinavir, nelfinavir, fosamprenavir, saquinavir, atazanavir with and without ritonavir, lopinavir/r. They should be conducted in small numbers of HIV+ patients before efficacy data is collected. For example, would the Boehringer Ingelheim BI 1182.51 study have shown the same results in a shorter sub-study - to see that there were some serious interaction issues between tipranavir/r and (all) other PIs?)
- ARVs not yet approved, as soon as there is dosing.
- Methadone
- Hormonal Contraceptives - oral, patch, and topical delivery of progestational and combined estrogen/progestational agents)
- Lipid regulators (statins, fibrates)
- Food and liquid - what kind of food, how much food, water intake

Within 6 months of approval:

- Ribavirin
- Ulcer drugs (H2 receptor antagonists, Proton Pump Inhibitors)
- Certain herbal medications & supplements (Appendix 1)
- Antipsychotics, ie, chlorprothixen, zuclopenthixol, haloperidol, etc
- Seizure drugs, ie, anti-epileptics, anti-convulsants
- Erectile dysfunction drugs, ie, sildenafil, tadalafil, vardenafil

Within 12 months of approval:

- Street drugs (ecstasy, methamphetamine, heroin) – these studies can be undertaken safely and legally in The Netherlands, Switzerland, Spain
- TB drugs (rifampin, rifabutin)
- Pegylated interferon
- Cardiac Drugs, ie, amiodaron, disulfiram, verapamil, beta blockers, etc
- Antibacterials, ie, roxythomicin, clindamycin, etc
- Anti-depressants, ie, bupropion, SSRIs, trazodone, TCAs, etc
- Hypnotics, ie, the non-benzodiazepine selective agonists of the GABA-A receptor complex, as well as benzodiazepines, flurazepam, zaleplon, diazepam, etc
- Antihistamines, ie, levocetirizine, loratadine, cetirizine, promethazine, etc
- Anti-fungals, ie, fluconazole, itraconazole, ketoconazole, voriconazole
- Broncho-dilatators
- Immunosuppressants, ie, cyclosporin A
- Antimalarials
- Uricostatics, ie, allopurinol

- Cytotoxic drugs, ie, tamoxifen, paxlitacel, vincristine, etc
- Complementary and alternative medicines. Because the list is extensive, we might suggest starting with the most commonly used according to FDA's Center for Food Safety and Applied Nutrition (www.cfsan.fda.gov). Appendix 1 lists some very commonly used CAMs seen at a recent PK meeting.

Not enough information is generated on specific sub-populations within the population of HIV patients that may use the drug at time of approval. We reiterate some common points here below, answers to which are needed more so now than ever before:

Specific Populations

- Gender percentages that more realistically reflect the population in which the drug is studied, ie, in the US there should be at least 30% women in all trials, including phase I and II pharmacokinetic trials.
- Ethnic and racial differences, again to reflect the epidemic itself.
- People with hepatic and renal insufficiency, especially those with HCV and/or HBV co-infection. For patients with mild liver impairment, are dose reductions needed / recommended? Ditto for those with more serious liver problems? Should more visits and laboratory analyses be performed on people with abnormal LFTs at baseline, including those with chronic hepatitis?
- Pediatrics / Pregnant women data is rarely generated. Bioequivalence is often not demonstrated for a powder / liquid formulation, if there is one. Pediatric formulations need to be devised and studied in both newborns and infants. Most ARVs are defined as Class C for pregnancy; they have unknown placental passage (newborn:mother drug ratio), and often long after full FDA approval, long-term animal carcinogenicity studies are still not done; along with the post-marketing pregnancy registry, ARVs need to be studied and categorized for use in pregnant women.
- Hyperbilirubinemia and other hepatic abnormalities need to be better characterised in drugs to be approved before approval.

There is an overdue role for well-planned and rigorous population PK in Phase III studies. Would the use of therapeutic drug monitoring (TDM) be helpful in managing different patients and patient populations? Studies to look at re-dosing via TDM in overdosed / underdosed patients need to be addressed. Can TDM be a useful tool in finding a dose that balances efficacy and toxicity? (2)

Studies in HIV-negative volunteers may provide a more rapid and efficient way of obtaining the in vivo data for two- and three-way drug interactions. [It must be said that there are safety and ethical issues here as well as possible differences between HIV-negative and HIV-infected volunteers. For antiretrovirals likely to be in wide use, we recommend that as many ARV three-way interactions as possible be done before approval.] (3)

We consider that some of these studies, both the PK studies and the population studies, are important enough to somehow bind the marketing rights of a sponsor who does not carry them out. We are interested in further exploring what to do when a company does not offer all the data considered "minimal", without in any way keeping that drug from someone in a life or death situation. For example, were FDA to demand 30% women in all HIV trials, and another 20% of people with hepatic failure level C, what would happen

if that were not achieved? Why would it not be achieved if FDA mandated it?

There needs to be a regulatory requirement for drug interaction data not to withheld but released early as an issue of public safety. Transparency and better definition need to be the hallmarks of all studies. [We refer to our support of the AMA and the growing association of some 17 scientific journals to publish all studies, both positive and negative and new Open Access initiatives, like the Public Library of Science (www.plos.org).]

Thank you for your anticipated assistance. The community has been making the same PK / population requests of Industry for many, many years and greatly appreciate the agency's concern in providing Industry with direction in this regard. Please do not hesitate to contact me with questions or feedback.

Very truly yours,

Rob Camp
Antiretroviral Project Director
Treatment Action Group
Cc: Deputy Director Jeffrey Murray, M.D. HFD-530 301-827-2338 CRPII/Rm. N413

Appendix 1: Complementary and alternative medicines (CAM) (vitamins/minerals, homeopathy, herbal, other) commonly used need to be looked at with ARV therapy. Although we realize that FDA does not regulate CAMs, the interactions of these with ARVs would be very helpful and possibly preventative of complications. A large percentage of people living with HIV use many of the products listed below. A good example of why these products need to be studied is the indinavir/hypericin interaction, where the metabolism of indinavir is speeded up and lower blood levels are the result, with the raised risk of treatment failure and resistance:

Echinacea, Ginseng, Evening primrose oil, Brewer's yeast, Cannabis, Soy lecithin, Hepatoprotective products, Cat's claw, Aloe vera, Propolis, Pollen, Bach's flowers, St John's wort (hypericin), Garlic supplements, Algae, Kombucha, Supplements such as zinc, selenium, vitamins, melatonin, carnitine, Co-Q, etc (4)

Refs: 1. Identifying metabolic differences in patient groups based on genetic polymorphism, or on other readily identifiable factors, such as age, race, and gender, can aid in interpreting results.

The effects of an investigational drug on the metabolism of other drugs and the effects of other drugs on an investigational drug's metabolism should be assessed relatively early in drug development so that the clinical implications of interactions can be assessed as fully as possible in later clinical studies.

- from FDA Guidance for Industry Population Pharmacokinetics, CDER and CBER, Feb1999

Identifying metabolic differences in patient groups based on genetic polymorphisms, or on other readily identifiable factors such as age, race, and gender, could help guide the design of dosimetry studies for such populations groups. This kind of information also will provide improved dosing recommendations in product labeling, facilitating the safe

and effective use of a drug by allowing prescribers to anticipate necessary dose adjustments. Indeed, in some cases, understanding how to adjust dose to avoid toxicity may allow the marketing of a drug that would have an unacceptable level of toxicity were its toxicity unpredictable and unpreventable.

Two of the major clinical reasons, as previously mentioned, are (1) to identify all of the major metabolic pathways that affect the drug and its metabolites and (2) to anticipate the effects of the drug on the metabolism of other drugs. With these objectives in mind, an understanding of the metabolic profile of a drug in vitro would be useful prior to the initiation of phase 2 studies and is especially important before phase 3 trials, when a broader population will be studied. This knowledge would permit the efficient design of clinical dose/response, interaction, and special population studies and also would enable adequate attention to be given to patient variability and potential interactions in phase 2 and 3 studies.

- from FDA Guidance for Industry Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro, CDER and CBER, April 1997, <http://www.fda.gov/cder/guidance/clin3.pdf>, Issued, Posted 4/8/1997.

2. from FDA Guidance for Industry In Vivo Drug Metabolism / Drug Interaction Studies – Study Design, Data Analysis, and Recommendations for Dosage and Labeling, CDER and CBER, November 1999, <http://www.fda.gov/cder/guidance/2635fnl.htm>, Issued 11/24/99.

3. Jonathan Schapiro and Terrence Blaschke, personal communications to author during the 5th International Workshop on Clinical Pharmacology of HIV Therapy, 1-3 March 2004, Rome, I.

4. Partial list compiled from two posters (Meemken, abstr 4.12; Tuset, abstr 4.18) at the 5th International Workshop on Clinical Pharmacology of HIV Therapy, 1-3 March 2004, Rome, I.

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