National PBM Drug Monograph

Darunavir (Prezista)

January 2007

VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

Executive Summary:

Indication:
Darunavir is a HIV-1 protease inhibitor. It is currently indicated for the treatment of HIV-1 infection, with concomitant ritonavir and other antiretroviral drugs, in treatment-experienced patients, such as those with HIV-1 strains resistant to more than one protease inhibitor.

Dosing:
The recommended dosing regimen for darunavir is 600mg administered concomitantly with 100mg of ritonavir twice daily with food.

Efficacy:
Robust efficacy results from Phase IIb and Phase III clinical trials evaluating darunavir/ritonavir versus other protease inhibitors in highly treatment-experienced patients led to the approval of darunavir. All response parameters in the POWER 1 and POWER 2 individual analyses were significantly better ($p < 0.001$) for darunavir/ritonavir when compared with patients receiving an investigator-selected protease inhibitor in the control arm. Darunavir response rates in Phase IIb studies POWER 1 and POWER 2 were affected by both specific mutations and the number of baseline mutations, as well as the number of active drugs in the optimized background regimen. The presence of baseline mutations V32I, I47V, or I54L or M, was associated with a decreased virologic response and decreased susceptibility to darunavir. In cell cultures, viruses with known resistance to other protease inhibitors were susceptible to darunavir. In clinical trials, 60% of patients with decreased susceptibility to tipranavir at baseline had a $\geq \log_{10}$ decrease in viral load at week 24 on darunavir and 36% reached < 50 HIV copies/mL.

Safety:
The most common adverse effects reported in clinical trials (> 10%) were diarrhea, nausea, headache, and nasopharyngitis. Severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, was reported in clinical trials. Rash (all grades, regardless of causality) occurred in 7% of patients treated with darunavir. The discontinuation rate due to rash was 0.3%. The overall rate of discontinuation of therapy due to adverse events was 9% in subjects receiving darunavir, while 5% of subjects in the comparator protease inhibitor arm discontinued therapy due to adverse events. The most common lab abnormalities in clinical trials evaluating darunavir/ritonavir versus a comparator protease inhibitor included ALT elevations > 2.5 x ULN (10% vs. 13%), AST elevations > 2.5 x ULN (6.9% vs. 9.8%), pancreatic amylase > 1.5 x ULN (16.9% vs. 8.9%), and pancreatic lipase 1.5 x ULN (8.5% vs. 4.1%). Darunavir contains a sulfa moiety and should be used with caution in patients with a documented sulfa allergy.

Drug Interactions:
Darunavir and ritonavir are CYP3A inhibitors. Increased plasma concentrations of drugs metabolized through CYP3A may occur when co-administered with darunavir and ritonavir. Co-administration of darunavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These medications are terfinadine, astemizole, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, and triazolam

Recommendations:

Darunavir should only be used in heavily treatment-experienced HIV patients with limited treatment options. At this time, darunavir should be considered for formulary status with restrictions to infectious disease specialists ensure appropriate use.

Introduction

The purposes of this monograph are to (1) evaluate the available evidence of safety, tolerability, efficacy, cost, and other pharmaceutical issues that would be relevant to evaluating darunavir for possible addition to the VA National Formulary; (2) define its role in therapy; and (3) identify parameters for its rational use in the VA.

Pharmacology/Pharmacokinetics[1,2]

Darunavir is a HIV-1 protease inhibitor. It prevents the formation of mature virus particles by selectively inhibiting the cleavage of HIV encoded Gag-Pol polyproteins in infected cells.

Parameter	Drug
Metabolism	Undergoes extensive oxidative metabolism Primarily metabolized by CYP450 enzymes in the liver, particularly CYP3A
Elimination	Primarily in the feces (79.5%), renal excretion accounts for 13.9%
Half-life	Terminal half-life is 15 hours when administered with ritonavir
Protein Binding	Approximately 95% of darunavir is protein bound, primarily to alpha 1-acid glycoprotein
Bioavailability	37% when administered alone 82% when co-administered with 100mg ritonavir twice daily

Darunavir should only be used in combination with 100mg of ritonavir to achieve sufficient plasma concentrations of darunavir. When a single dose of 600mg of darunavir was administered with 100mg of ritonavir twice daily, there was a 14-fold increase in systemic exposure of darunavir.

FDA Approved Indication(s) and Off-label Uses[1,2]

Darunavir is indicated for the treatment of HIV-1 infection, with concomitant ritonavir and other antiretroviral drugs, in treatment-experienced patients, such as those with HIV-1 resistant strains to at least one protease inhibitor. The following points should be considered when initiating therapy with darunavir:

- Treatment history and, when available, genotypic or phenotypic testing, should guide the use of darunavir
- The use of other active agents with darunavir is associated with a greater likelihood of treatment response
- The risks and benefits of darunavir have not been established in treatment-naïve adult patients or pediatric patients.

Current VA National Formulary Status

	Indinavir	Saquinavir	Lopinavir/ ritonavir	Fosamprenavir	Ritonavir	Atazanavir	Nelfinavir
Formulary	X	X	X	X	X	X	X
Non-Formulary							

Dosage and Administration[1,2]

The recommended dosage of darunavir is 600mg (two 300mg tablets) twice daily taken along with ritonavir 100mg twice daily with food. The type of food does not affect the absorption of darunavir. When administered with food, the AUC and Cmax of darunavir, administered along with ritonavir, was approximately 30% greater than when administered in the fasting state.

Population pharmacokinetic analysis revealed higher mean darunavir exposure in females (16.8%) in females with HIV compared to males, though this finding is not clinically significant.

Pharmacokinetic analysis found that race, age (18-75 years old), and co-infection with hepatitis B or C did not affect darunavir pharmacokinetics.

Hepatic Impairment: Darunavir has not been studied in patients with varying degrees of hepatic impairment. Darunavir is primarily metabolized by the liver. Caution should be used when darunavir is given to patients with hepatic impairment. Increased plasma concentrations are expected in patients with hepatic impairment.

Renal Impairment: Population pharmacokinetic analysis showed that the pharmacokinetics of darunavir were not significantly affected by moderate renal impairment (CrCl 30-60 mL/min). There is no data available in patients with severe renal impairment or end-stage renal failure.

Dialysis: Darunavir and ritonavir are highly bound to plasma proteins; therefore it is unlikely that they will be significantly removed by hemodialysis or peritoneal dialysis.

Adverse Events (Safety Data)

Common Adverse Events[1-5]

In the POWER 1 and POWER 2 studies, the most common treatment-emergent adverse events reported in patients receiving darunavir therapy were diarrhea (19.8% and 28.2%, respectively), nausea (18.3% and 12.9%), headache (15.3% and 20.2%), and nasopharyngitis (13.7% and 10.5%).

Percentage of Subjects with Treatment-Emergent Adverse Effects in > 2% of Adult Subjects			
System Organ Class	**Randomized Studies POWER 1 and POWER 2 Trials**		**Non-Randomized POWER 3 Analysis**
	Darunavir/Ritonavir 600mg/100mg bid (N=131)	**Comparator Protease Inhibitor (N = 124)**	**Darunavir/Ritonavir 600mg/100mg bid (N = 327)**
Gastrointestinal Disorders			
Diarrhea	2.3%	3.2%	2.8%
Vomiting	1.5%	1.6%	2.4%
Abdominal Pain	2.3%	0.8%	1.2%
Constipation	2.3%	0.8%	0.6%
Nervous System Disorders			
Headache	3.8%	2.4%	0.9%

Other Adverse Events[1,2]

Treatment-Emergent Adverse Effects Occurring in < 2% of Patients Receiving Darunavir (n=458)	
Body System	**Adverse Event**
Body as a Whole	Folliculitis, asthenia, pyrexia, fatigue, rigors, hyperthermia, peripheral edema
Cardiovascular System	Myocardial infarction, tachycardia, hypertension
Digestive System	Flatulence, abdominal distension, dry mouth, dyspepsia, abdominal pain, constipation
Metabolic/Nutritional Disorders	Anorexia, hypercholesterolemia, hyperlipidemia, diabetes mellitus, decreased appetite, obesity, fat redistribution, hyponatremia, polydipsia
Musculoskeletal System	Arthralgia, pain in extremity, myalgia, osteopenia, osteoporosis
Nervous System	Peripheral neuropathy, hypoesthesia, memory impairment, parasthesia, somnolence, transient ischemic attack, confusional state, disorientation, irritability, altered mood, nightmare, anxiety, headache
Respiratory System	Dyspnea, cough, hiccups
Skin and Appendages	Lipoatrophy, night sweats, allergic dermatitis, eczema, toxic skin eruption, alopecia, dermatitis medicamentosa, hyperhidrosis, skin inflammation, maculopapular rash, erythema multiforme, Stevens-Johnson Syndrome
Special Senses	Vertigo
Urogenital System	Acute renal failure, renal insufficiency, nephrolithiasis, polyuria, gynecomastia

Deaths and Other Serious Adverse Events[1,2]

- Skin Rash: Severe skin rash, including erythema multiforme and Stevens-Johnson Syndrome, was reported during clinical trials. In clinical trials (n=924), rash of all grades, regardless of causality, occurred in 7% of patients treated with darunavir. One case of Stevens-Johnson Syndrome was reported in a phase 3 study of treatment naïve patients receiving darunavir/ritonavir 800mg/100mg daily. The discontinuation rate in due to rash in clinical trials was 0.3%.
- Death: In the two controlled studies (Power 1 and Power 2), 17 of 513 DRV/r subjects died reflecting a mortality rate of 3.9 per 100 patient-years of follow-up compared to 0/124 control subjects. Reported causes of death were similar to those observed in advanced populations of HIV-infected patients. Patients who died had more advanced disease relative all subjects enrolled. Deaths in other clinical trials of darunavir/ritonavir will be monitored closely for any imbalances.

Effects on Lab Results[1,2]

Treatment Emergent Laboratory Abnormalities Reported in ≥ 2% of Subjects				
		Randomized Studies POWER 1 and POWER 2		Non-Randomized POWER 3 Study
Laboratory Parameter	Limit	Darunavir/r 600/100mg BID n=131	Comparator PI n=124	Darunavir/r 600/100mg BID n=327
Aspartate Aminotransferase	> 2.5 x ULN	10%	13%	5.3%
Alanine Aminotransferase	> 2.5 x ULN	6.9%	9.8%	5.6%
Gamma Glutamyl Transferase	> 2.5 x ULN	9.2%	8.9%	8.4%
Hyperbilirubinemia	> 1.5 x ULN	2.3%	15.4%	0.9%
Alkaline Phosphatase	> 2.5 x ULN	4.6%	0%	2.8%
Pancreatic Amylase	> 1.5 x ULN	16.9%	8.9%	10.8%
Pancreatic Lipase	1.5 x ULN	8.5%	4.1%	6.2%
Hyperglycemia	~ 161mg/dL	2.3%	8.1%	5.9%
Hypoglycemia	~ 54mg/dL	1.5%	1.6%	3.7%
Total Cholesterol	~240mg/dL	9.2%	3.3%	8%
Triglycerides	> 400mg/dL	25.4%	26%	18.9%
Hypoalbuminemia	< 3g/dL	3.1%	1.6%	4.3%
Hyperuricemia	~9.9mg/dL	6.9%	6.5%	2.2%
Bicarbonate	< 15mmol/L	3.1%	4.1%	3.4%
Hypocalcemia	~7.8mg/dL	0%	0.8%	4%
Hyponatremia	~129mEq/L	0.8%	0%	2.5%
Hypernatremia	~151mEq/L	2.3%	0%	0%

Tolerability:[1,2]

In randomized trials, the rates of discontinuation of therapy due to adverse events were 9% in subjects receiving darunavir and 5% in subjects in the comparator protease inhibitor arm.

Precautions/Contraindications[1,2]

Precautions

- Darunavir must be co-administered with ritonavir and food. Failure to correctly administer darunavir will result in plasma concentrations that are insufficient to produce the desired antiviral effect.
- Pregnancy Category B

- Mothers should be instructed to not breastfeed while receiving darunavir. Although it is unknown whether darunavir is secreted in human breast milk, it has been detected in the milk of lactating rats.
- Darunavir and ritonavir are CYP3A inhibitors. Increased plasma concentrations of drugs metabolized through CYP3A may occur when co-administered with darunavir and ritonavir.
- Darunavir contains a sulfa moiety and should be used with caution in patients with a documented sulfa allergy.
- Increased bleeding, including spontaneous skin hematomas and hemarthrosis has been reported in patients with hemophilia A and B treated with protease inhibitors.
- Darunavir may decrease hormonal levels in patients receiving estrogen-based contraceptives. Patients should be advised to use another form of birth control while receiving darunavir.
- Severe skin rashes, including Stevens-Johnson syndrome, have been reported with darunavir use. In clinical trials (n=924), rash (all grades, regardless of causality) occurred in 7% of patients treated with darunavir.
- New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during post-market surveillance of HIV protease inhibitors. Some patients required initiation or adjustment of insulin or oral hypoglycemic agents. There have been reported cases of diabetic ketoacidosis in patients receiving HIV protease inhibitors.
- Redistribution/accumulation of body fat, including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid appearance" have been observed in patients receiving antiretroviral therapy. A casual relationship has not been determined.
- During the initial phase of treatment, patients responding to antiretroviral therapy may develop an inflammatory response to indolent or residual opportunistic infections, such as *Mycobacterium avium* complex, cytomegalovirus, *Pneumocystis jiroveci* pneumonia, and tuberculosis. This may necessitate further evaluation and treatment.

Contraindications

- Darunavir is contraindicated in patients with known hypersensitivity to any of the ingredients of the product
- Co-administration of darunavir is contraindicated with drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These medications are terfinadine, astemizole, dihydroergotamine, ergonovine, ergotamine, methylergonovine, cisapride, pimozide, midazolam, and triazolam.

Look-alike / Sound-alike Error Risk Potential

The VA PBM and Center for Medication Safety is conducting a pilot program which queries a multi-attribute drug product search engine for similar sounding and appearing drug names based on orthographic and phonologic similarities, as well as similarities in dosage form, strength and route of administration. Based on similarity scores as well as clinical judgment, the following drug names may be potential sources of drug name confusion:

LA/SA for generic name darunavir: abacavir 300mg tablet, Denavir 0.1% cream, tenofovir 300mg tablet, Trizivir 300mg tablet, Anabar 300mg tablet, Combivir 300mg tablet, Epivir 300mg tablet, Retrovir 300mg tablets, indinavir 100mg capsule, and daunorubicin 2mg injection.

LA/SA for trade name Prezista: Evista 60mg tablets, prazosin 1mg capsule, Pronestyl 250mg tablet, Pexeva 30mg tablet, and Trizivir 300mg tablet.

Drug Interactions[1,2]

Drug-Drug Interactions

DRUGS THAT SHOULD NOT BE CO-ADMINISTERED WITH DARUNAVIR	
Drug Class: Drug Name	**Clinical Significance**
Anticonvulsants:	Carbamazepine, phenobarbital, phenytoin are

Carbamazepine, Phenobarbital, Phenytoin	inducers of CYP450 enzymes. Co-administration of these medications with darunavir may cause significant decreases in darunavir plasma concentrations. This may result in loss of darunavir effectiveness.
Antihistamines: Astemizole, Terfenadine	Co-administration of astemizole or terfenadine with darunavir is **contraindicated** due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterials: Rifampin	Rifampin is a potent inducer CYP450 metabolism. Rifampin should not be co-administered with darunavir due to the potential for decreased darunavir plasma concentrations. This may result in loss of darunavir effectiveness.
Ergot Derivatives: Dihydroergotamine, Ergonovine, Ergotamine, Methylergonavine	Co-administration of dihydroergotamine, ergonovine, ergotamine, or methylergonavine with darunavir is **contraindicated** due to the potential for serious and/or life-threatening such as acute ergot toxicity (characterized by peripheral vasospasm and ischemia of extremities and other tissues).
Gastrointestinal Motility Agents: Cisapride	Co-administration of cisapride and darunavir is **contraindicated** due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's Wort (*Hypericum perforatum)*	Products containing St. John's Wort should not be used concomitantly with darunavir due to the potential for decreased darunavir plasma concentrations. This may results in loss of darunavir effectiveness.
HMG-CoA Reductase Inhibitors: Lovastatin, Simvastatin	Lovastatin and simvastatin should not be co-administered with darunavir due to the potential risk of serious adverse reactions such as myopathy, including rhabdomyolysis.
Neuroleptics: Pimozide	Co-administration of pimozide and darunavir is **contraindicated** due to the potential for serious and/or life threatening reactions such as cardiac arrhythmias.
Sedative/Hypnotics: Midazolam, Triazolam	Co-administration of midazolam or triazolam and darunavir is **contraindicated** due to the potential for serious and/or life threatening reactions such as prolonged or increased sedation or respiratory depression.

ESTABLISHED AND OTHER POTENTIALLY SIGNIFICANT DRUG INTERACTIONS		
Drug Class: Drug Name	**Effect on Drug Concentrations**	**Clinical Significance**
HIV-Antiviral Agents: Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)		
Efavirenz	↓ Darunavir ↑ Efavirenz	The combination of darunavir and efavirenz should be used with caution. Co-administration of darunavir and efavirenz resulted in a decrease of 13% in the AUC of darunavir and a 33% decrease in the Cmin. The AUC of efavirenz increased by 21% and Cmin increased by 17%.
HIV-Antiviral Agents: Protease Inhibitors (PIs)		
Indinavir	↑ Darunavir	The appropriate dose of indinavir in combination with darunavir has

	↑ Indinavir	not been established.
Lopinavir/Ritonavir	↓ Darunavir ↑ Lopinavir	Co-administration of lopinavir/ritonavir and darunavir is not recommended. When used in combination, there was a 53% decrease in the AUC of darunavir.
Saquinavir	↓ Darunavir ↔ Saquinavir	Co-administration of saquinavir and darunavir is not recommended. When used in combination, there was a 26% decrease in the AUC of darunavir.
Other Agents:		
Anti-Arrhythmics: Bepridil, Lidocaine (systemic), Quinidine, Amiodarone	↑ Anti-Arrhythmics	Bepridil, lidocaine, quinidine, and amiodarone plasma concentrations may increase when co-administered with darunavir. Caution is warranted and therapeutic concentration monitoring is recommended, when available, for anti-arrhythmics.
Anticoagulants: Wafarin	↓ Warfarin	Warfarin plasma concentrations may be affected when co-administered with darunavir. It is recommended to monitor the INR closely when concomitantly using these two agents.
Antidepressants: Trazodone	↑ Trazodone	Co-administration of trazodone and darunavir may result in increased plasma concentrations of trazodone. Caution should be used if trazodone is administered with darunavir. A lower dose of trazodone should be considered.
Anti-Infective: Clarithromycin	↑ Clarithromycin	In patients with normal renal function, no dosage adjustment is required for clarithromycin or darunavir. In patients with renal impairment, the following adjustments are recommended: • CrCl 30-60mL/min: reduce clarithromycin dose by 50% • CrCl < 30mL/min: reduce clarithromycin dose by 75%
Antifungals: Ketoconazole, Itraconazole, Voriconazole	↑ Darunavir ↑ Ketoconazole ↑ Itraconazole (not studied) ↓ Voriconazole (not studied)	Ketoconazole and itraconazole are potent inhibitors and substrates of CYP3A. Co-administration of these medications with darunavir may result increased plasma concentrations of darunavir. Co-administration of darunavir and ketoconazole and itraconazole may result in increased plasma concentrations of ketoconazole and itraconazole. When co-administration is

		required, the daily dose of ketoconazole or itraconazole should not exceed 200mg. Co-administration of voriconazole and darunavir has not been studied. Voriconazole has been studied in combination with ritonavir, which is administered with darunavir. When co-administered, ritonavir decreased the AUC of voriconazole by an average of 39%. Voriconazole should not be co-administered with darunavir unless an assessment of the risk/benefit ratio justifies the use of voriconazole.
Antimycobacterial: Rifabutin	↓ Darunavir ↑ Rifabutin	Rifabutin is an inducer and substrate for CYP3A. Co-administration of rifabutin and darunavir is expected to increase the plasma concentrations of rifabutin and decrease darunavir concentrations. When used concomitantly, it is recommended to administer rifabutin at a dosage of 150mg every other day.
Calcium Channel Blockers: Felodipine, Nifedipine, Nicardipine	↑ Calcium Channel Blockers	Plasma concentrations of calcium channel blockers may increase when co-administered with darunavir. Caution is warranted and clinical monitoring of patients is recommended.
Corticosteroids: Dexamethasone, Fluticasone propionate	↓ Darunavir ↑ Fluticasone propionate	Use with caution. Systemic dexamethasone induces CYP3A and can therefore decrease darunavir plasma concentrations. Concomitant use of darunavir and inhaled fluticasone propionate may result in increased plasma concentrations of fluticasone propionate. Alternatives should be considered, especially for long-term use.
HMG-CoA Reductase Inhibitors: Atorvastatin, Pravastatin	↑ Atorvastatin ↑ Pravastatin	When atorvastatin is co-administered with darunavir, it is recommended to start at the lowest possible dose of atorvastatin. Careful monitoring of the patient is warranted. A gradual increase in atorvastatin dose may be considered based on the clinical response. When pravastatin was co-administered with darunavir, the AUC of pravastatin increased an average of 81%. In some patients with AUC increased 5-fold. The

		mechanism of this interaction is not known.
Immunosuppressants: Cyclosporine, Tacrolimus, Sirolimus	↑ Immunosuppressants	Plasma concentrations of cyclosporine, tacrolimus, or sirolimus may increase when co-administered with darunavir. Plasma concentration monitoring of immunosuppressants is recommended when used concomitantly with darunavir.
Narcotic Analgesics: Methadone	↓ Methadone	When methadone is used concomitantly with darunavir, patients should be monitored for opiate abstinence syndrome. Ritonavir, which must be co-administered with darunavir, is known to induce the metabolism of methadone. An increase in methadone dosage may be considered based on clinical response.
Oral Contraceptives: Ethinyl estradiol, Norethindrone	↓ Ethinyl estradiol ↓ Norethindrone	Alternative or additional contraceptive measures should be used when estrogen-containing contraceptives are used concomitantly with darunavir. Plasma concentrations of ethinyl estradiol may decrease due to induction of its metabolism by ritonavir, which must be co-administered with darunavir.
PDE-5 Inhibitors: Sildenafil, Vardenafil, Tadalafil	↑ PDE-5 inhibitors	PDE-5 inhibitors should be used with caution when co-administered with darunavir. If concomitant use is required, the following dose adjustments are recommended: • Sildenafil – single dose not exceeding 25mg in 48 hours • Vardenafil – single dose not exceeding 2.5mg in 72 hours • Tadalafil – single dose not exceeding 10mg in 72 hours
Selective Serotonin Reuptake Inhibitors (SSRIs): Sertraline, Paroxetine	↔ Darunavir ↓ Sertraline ↓ Paroxetine	If sertraline or paroxetine is co-administered with darunavir, the recommended approach is careful titration of the SSRI dose based on a clinical assessment of antidepressant response. Patients on stable doses of sertraline or paroxetine who start darunavir should be monitored for antidepressant response.

Efficacy Measures

Efficacy Endpoints[3-7,9-10]

The primary efficacy endpoint in the POWER 1 and POWER 2 trials was the proportion of patients achieving a ≥ 1 $\log_{10}$ reduction from baseline viral load at Week 24. Secondary endpoints included changes from baseline in $\log_{10}$ viral load and CD4 cell count, and the proportion of patients achieving undetectable viral loads (viral load < 50 copies/mL). The primary efficacy endpoint in the POWER 3 trial was the proportion of patients achieving ≥ 1 $\log_{10}$ reduction in HIV RNA by week 24. Other analyses included change in CD4 count and the impact of baseline characteristics (darunavir fold change (FC), CD4 count, number of primary protease inhibitor mutations, number of susceptible nucleoside reverse transcriptase inhibitors (NRTIs), in the OBR, use of the fusion inhibitor enfuvirtide, and prior use of tipranavir) on treatment response (achieving reduction of HIV RNA to < 50 copies/mL. Safety data included clinical and laboratory adverse events graded by their severity and relation to darunavir

Summary of Efficacy Findings[3-7,9-10]

All response parameters in the POWER 1 and POWER 2 individual analyses were significantly better ($p < 0.001$) for darunavir/ritonavir when compared with patients receiving an investigator-selected protease inhibitor in the control arm. In the pooled analysis of the Week 24 data, there were significantly higher proportions of patients in the darunavir/ritonavir group (70%) compared to the control group (21%) who reached the primary endpoint of HIV-1 RNA decrease of at least 1 $\log_{10}$ from baseline ($p < 0.001$). The overall change in HIV-1 RNA from baseline was -1.89 $\log_{10}$ copies/mL for the darunavir/ritonavir 600mg/100mg BID group. The control group experienced a -0.48 $\log_{10}$ copies/mL change from baseline. The difference between the control group and the darunavir/ritonavir group was statistically significant ($p < 0.001$). There were 26% virologic failures in the darunavir/ritonavir group compared with 71% in the control group. A statistically significant ($p < 0.001$) percentage of patients achieved undectability (< 50 copies/mL) in the darunavir/ritonavir group (45%) when compared to the control group (12%) at Week 24. The immunologic response observed in darunavir/ritonavir patients was also statistically superior to that observed in the control group. A mean CD4 increase of 92 cells/μL was attained in the darunavir/ritonavir group compared to a mean increase of 17 CD4 cells/μL in the control group ($p < 0.001$). In the POWER 3 trial, 65% of patients receiving darunavir/ritonavir 600mg/100mg twice daily achieved a ≥ log10 reduction from baseline viral load at week 24. The data collected from the POWER 3 trial confirmed and supported the observations from the POWER 1 and POWER 2 trials in respect to the same darunavir/ritonavir regimen. POWER 3 also found that the number of PI mutations was poorly correlated with virologic response to darunavir/ritonavir.

Genotypic and Phenotypic Analysis[8]

Baseline genotypic and phenotypic analysis of virus may aid in determining darunavir susceptibility before initiation of therapy. Several analyses were conducted to evaluate the impact of specific base-line protease inhibitor resistance-associated mutations at baseline of virologic response. Darunavir response rates in Phase IIb studies POWER 1 and POWER 2 were affected by both specific mutations and the number of baseline mutations. The presence of baseline mutations V32I, I47V, or I54L or M, was associated with a decreased virologic response to darunavir. These mutations were also associated with decreased susceptibility to darunavir. Diminished response to darunavir was also observed in patients with ≥ 7 protease inhibitor resistance-associated mutations at baseline. Of viruses isolated from patients experiencing virologic failure on darunavir/ritonavir, more that 50% were still sensitive to tipranavir while less than 5% were sensitive to other PIs.

Response to Darunavir by Baseline Number of Protease Inhibitor Resistance-Associated Mutations: As Treated Analysis of Studies POWER 1 and POWER 2[1]

	Darunavir/ritonavir 600mg/100mg bid (n=125)				Comparative Arm (n=1200)			
PI Mutations	**n**	**Proportion of subjects with ≥ 1 $\log_{10}$ decrease at**	**Proportion of subjects with < 50 copies/mL at Week 24**	**Median $DAVG_{24}$**	**n**	**Proportion of subjects with ≥ 1 $\log_{10}$ decrease at**	**Proportion of subjects with < 50 copies/mL at Week 24**	**Median $DAVG_{24}$**

		Week 24				**Week 24**		
0-4	57	81%	46%	-2.16	52	23%	13%	-0.57
5-6	54	67%	52%	-2.13	51	24%	16%	-0.43
≥ 7	14	21%	14%	-0.87	17	6%	0%	-0.13

Baseline darunavir phenotype was shown to be a predictive factor of virologic outcome. The data is not meant to represent definitive clinical susceptibility breakpoints for darunavir, but rather to give clinicians information on the likelihood of virologic success based on pre-treatment susceptibility to darunavir in protease inhibitor –experienced patients.

Response to Darunavir/Ritonavir 600mg/100mg bid by Baseline Darunavir Phenotype: As-Treated Analysis of Studies POWER 1, POWER 2, and POWER 3[1]			
Baseline Darunavir Phenotype N = 340 (fold change ranges)	**Proportion of subjects with ≥ 1 log_{10} decrease at Week 24**	**Proportion of subjects with < 50 copies/mL at Week 24**	**Clinical Response Range**
All Ranges	70% 238/340	43% 147/340	Overall Response
0-2	88% 119/136	60% 82/136	Higher than Overall Response
> 2-7	73% 62/85	47% 40/85	Similar to Overall Response
> 7-30	53% 33/63	24% 15/63	Lower than Overall Response
> 30	43% 24/56	18% 10/56	Lower than Overall Response

Clinical Trials[3-9]

Patient Characteristics

Patient Baseline Characteristics				
	POWER 1		**POWER 2**	
	600mg darunavir/100mg ritonavir (n=65)	Control Protease Inhibitor (n=63)	600mg darunavir/100mg ritonavir (n=66)	Control Protease Inhibitor (n=61)
Demographics				
Male (%)	85	87	94	89
Mean age (years)	42	43	46	46
Caucasian (%)	89	83	73	62
Duration of infection (mean years)	11.1	12.1	12.9	14.1
VL (mean log_{10} copies/mL)	4.6	4.4	4.6	4.6
CD4 (median cells/μL)	176	197	115	113
Baseline Characteristics				
PI Mutations (median)				
Primary	2	3	3	3
Resistance-Associated	8	8	8	8
All	18	17	18	17
% of Patients with Prior use of Enfuvirtide	11	10	27	23

POWER 3 Study:
327 patients were enrolled an initiated on darunavir/ritonavir 600mg/100mg twice daily treatment. 303 of these patients had not participated in a prior darunavir study. The remaining 24 had rolled over from the control arm of previous darunavir studies after experiencing virologic failure. The mean age of the study population was 44 years. The majority of patients were male (87%) and/or Caucasian (75%). 98% of participants had experience with at least two PIs, one NNRTI, and four NRTIs. Patients had a median of three primary PI mutations. Only 20% of the patients were sensitive to another approved PI at screening, at which time tipranavir was not available. Median viral load at baseline was 4.6 log_{10} copies/mL, while CD4 counts averaged 115 cells/μL. Tipranavir and enfuvirtide had been used previously by 31% and 30% of patients, respectively. This patient population was more similar to the patient population used in POWER 2 than POWER 1.

Citation	Katlama C, Carvalho M, Cooper D. et al. TMC114/r outperforms investigator-selected PIs in 3-class-experienced patients: week 24 primary efficacy analysis of POWER 1 (TMC114-C213). Poster presented at the 3rd International AIDS Society (IAS) Conference on HIV Pathogenesis and Treatment; 2005 July 24-27; Rio de Janeiro, Brazil. Grinsztejn B, Arasteh K, Clotet B, et al. TMC114/r is well tolerated in 3-class-experienced patients: week 24 primary safety analysis of POWER 1 (TMC114-C213). Poster presented at the 3rd IAS Conference on HIV Pathogenesis and Treatment 2005 July 24-27; Rio de Janeiro, Brazil.
Study Goals	To evaluate the safety and efficacy of darunavir plus ritonavir in three-class antiretroviral treatment-experienced patients with HIV-1 infection
Methods	**Study Design** The POWER 1 study was a randomized, controlled, partially-blind, international, multicenter, Phase IIb dose-finding study. Included subjects were randomized to receive either darunavir/ritonavir 600mg/100mg bid + an optimized background regimen (OBR), darunavir/ritonavir 400mg/100mg bid + OBR, darunavir/ritonavir 800mg/100mg QD + OBR, darunavir/ritonavir 400mg/100mg QD + OBR, or an investigator selected protease inhibitor + OBR (designated the control group). The optimized background regimen included 2 nucleoside revere transcriptase inhibitors with or without the fusion inhibitor enfurvirtide. Participants were stratified by the number of baseline PI mutations, baseline viral load, and prior use of enfuvirtide. The trial was 24 weeks in duration. The primary endpoint was the portion of patients achieving ≥ 1 $\log_{10}$ reduction in HIV copies/mL by week 24. Other efficacy endpoints were the proportion of patients achieving maximal viral suppression (defined as < 50 HIV copies/mL), mean $\log_{10}$ change in viral load (VL), and the change in the CD4 cell count. **Data Analysis** All analyses were intention-to-treat (ITT). Analysis of percent responders was performed using the time to loss of virologic response (TLOVR) algorithm. Change in HIV-1 RNA from baseline was performed using a noncompleter equal failure (NC = F) analysis and immunologic response was measured using a last observation carried forward (LOCF) analysis.
Criteria	**Inclusion criteria** Male and female subjects were included in the study if they were 18 years of age or older who had received at least three classes of antiretrovirals. Included subjects had been receiving a stable protease inhibitor-containing regimen for at least eight weeks prior to screening. Their plasma HIV-1 RNA had to be > 1,000 copies/mL. They also had to have at least one primary protease inhibitor mutation at screening, and have no CD4 cell count restrictions. Patients with Hepatitis B or C were allowed to enter the study. **Exclusion criteria** Not reported
Results	**Primary Endpoint:** *Proportion of patients achieving ≥ 1 $\log_{10}$ reduction in from baseline in viral load at Week 24:* • Darunavir/ritonavir 400mg/100mg QD: 70% • Darunavir/ritonavir 800mg/100mg QD: 72% • Darunavir/ritonavir 400mg/100mg BID: 69% • Darunavir/ritonavir 600mg/100mg BID: 77% • Control: 25% **Other Endpoints:** *Mean CD4 increase from baseline (cells/mm^3):* • Darunavir/ritonavir 400mg/100mg QD: 68 • Darunavir/ritonavir 800mg/100mg QD: 75 • Darunavir/ritonavir 400mg/100mg BID: 71 • Darunavir/ritonavir 600mg/100mg BID: 124 • Control: 20 *Mean viral load change from baseline ($\log_{10}$ copies/mL):* • Darunavir/ritonavir 400mg/100mg QD: -1.78 • Darunavir/ritonavir 800mg/100mg QD: -1.83 • Darunavir/ritonavir 400mg/100mg BID: -1.69 • Darunavir/ritonavir 600mg/100mg BID: -2.03 • Control: -0.63 *Proportion of patients with viral load < 50 copies/mL:* • Darunavir/ritonavir 400mg/100mg QD: 43% • Darunavir/ritonavir 800mg/100mg QD: 48%

	• Darunavir/ritonavir 400mg/100mg BID: 49% • Darunavir/ritonavir 600mg/100mg BID: 53% • Control: 18%
Conclusions	The authors concluded that 3-class-experienced patients treated with darunavir/ritonavir exhibited significantly greater viral suppression and CD4 response compared to patients who received control protease inhibitors and the viral suppression observed was comparable to that typically seen in less treatment-experienced patients. The darunavir/ritonavir 600mg/100mg BID dose resulted in the greatest overall antiretroviral effect.

Citation	Wilkin T, Haubrich R, Steinhart CR, et al. POWER 2 (TMC114-C202 study) Week 24 efficacy analysis. Presented at the 45th Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2005 December 16-19; Washington, DC. Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); 2005 December 16-19; Washington, D.C. Berger B, Bellos N, Farthing C, et al. TMC114/r in 3-class-experienced patients: 24-week primary safety analysis of the POWER 2 study (TMC114-C202). Poster presented at the 45th Annual ICAAC; 2005 December 16-19; Washington, D.C.
Study Goals	To evaluate the safety and efficacy of darunavir plus ritonavir in three-class antiretroviral treatment-experienced patients with HIV-1 infection
Methods	**Study Design** The POWER 2 study was a randomized, controlled, partially-blinded, international, multicenter, Phase IIb dose-finding study. Included subjects were randomized to receive either darunavir/ritonavir 600mg/100mg bid + an optimized background regimen (OBR), darunavir/ritonavir 400mg/100mg bid + OBR, darunavir/ritonavir 800mg/100mg QD + OBR, darunavir/ritonavir 400mg/100mg QD + OBR, or an investigator selected protease inhibitor + OBR (designated the control group). The optimized background regimen included 2 nucleoside revere transcriptase inhibitors with or without the fusion inhibitor enfurvirtide. Participants were stratified by the number of baseline PI mutations, baseline viral load, and prior use of enfuvirtide. The trial was 24 weeks in duration. The primary endpoint was the portion of patients achieving ≥ 1 log_{10} reduction in HIV copies/mL by week 24. Other efficacy endpoints were the proportion of patients achieving maximal viral suppression (defined as < 50 HIV copies/mL), mean log_{10} change in viral load (VL), and the change in the CD4 cell count **Data Analysis** All analyses were intention-to-treat (ITT). Analysis of percent responders was performed using the time to loss of virologic response (TLOVR) algorithm. Change in HIV-1 RNA from baseline was performed using a noncompleter equal failure (NC = F) analysis and immunologic response was measured using a last observation carried forward (LOCF) analysis.
Criteria	**Inclusion criteria** Male and female subjects were included in the study if they were 18 years of age or older who had received at least three classes of antiretrovirals. Included subjects had been receiving a stable protease inhibitor-containing regimen for at least eight weeks prior to screening. Their plasma HIV-1 RNA had to be > 1,000 copies/mL. They also had to have at least one primary protease inhibitor mutation at screening, and have no CD4 cell count restrictions. **Exclusion criteria** Patients with Hepatitis B or C co-infection were excluded. Other exclusion criteria were not reported.
Results	**Primary Endpoint:** *Proportion of patients achieving ≥ 1 log_{10} reduction in from baseline in viral load at Week 24:* • Darunavir/ritonavir 400mg/100mg QD: 45% • Darunavir/ritonavir 800mg/100mg QD: 49% • Darunavir/ritonavir 400mg/100mg BID: 54% • Darunavir/ritonavir 600mg/100mg BID: 62% • Control: 14% **Other Endpoints:** *Mean CD4 increase from baseline (cells/mm^3):* • Darunavir/ritonavir 400mg/100mg QD: 64 • Darunavir/ritonavir 800mg/100mg QD: 75 • Darunavir/ritonavir 400mg/100mg BID: 68 • Darunavir/ritonavir 600mg/100mg BID: 59 • Control: 12 *Mean viral load decrease (log_{10} copies/mL):* • Darunavir/ritonavir 400mg/100mg QD: -1.2 • Darunavir/ritonavir 800mg/100mg QD: -1.3 • Darunavir/ritonavir 400mg/100mg BID: -1.4 • Darunavir/ritonavir 600mg/100mg BID: -1.7 • Control: -0.3 *Proportion of patients with viral load < 50 copies/mL:* • Darunavir/ritonavir 400mg/100mg QD: 18% • Darunavir/ritonavir 800mg/100mg QD: 20%

	• Darunavir/ritonavir 400mg/100mg BID: 36% • Darunavir/ritonavir 600mg/100mg BID: 39% • Control: 7%
Conclusions	HIVR RNA and CD4 responses were superior in all darunavir/ritonavir groups compared with the control group. Darunavir/ritonavir was generally well tolerated in these treatment-experienced patients and was associated with a low rate of discontinuations due to adverse events. The overall safety profile of darunavir/ritonavir was similar to that in less disease-advanced patients (POWER 1). Darunavir/ritonavir doses selected for phase III trials were 600mg/100mg BID for treatment-experienced patients and 800mg/100mg QD for treatment-naïve patients.

Citation	De Meyer S, Hill A, De Baere I, et al. Effect of baseline susceptibility and on-treatment mutations on TMC114 and control PI efficacy. Preliminary analysis of data from PI-experienced patients from POWER 1 and POWER 2. Presented at the 13th Conference on Retroviruses and Opportunistic Infections (CROI); 2006b February 5-8; Denver, CO. Data on file, Tibotec Therapeutics. (Multivariate pooled analysis of potential prognostic factors from week 24 efficacy data from POWER 1 and POWER 2 trials).
Study Goals	To evaluate potential prognostic factors from Week 24 efficacy data from the POWER 1 and POWER 2 studies
Methods	**Study Design** This study was a multivariate pooled analysis of potential prognostic factors from Week 24 efficacy data from the randomized POWER 1 and POWER 2 trials. The POWER 1 and POWER 2 studies were randomized, controlled, partially-blinded, international multicenter, Phase IIb dose-finding studies. This study evaluated only those patients which receiving darunavir/ritonavir 600mg/100mg BID + OBR or the investigator-selected PI + OBR. The optimized background regimen included 2 nucleoside revere transcriptase inhibitors with or without the fusion inhibitor enfurvirtide. Patients were stratified according to enfuvirtide use, number of primary protease inhibitor mutations at baseline, and baseline viral load. The primary subanalysis was the proportion of patients achieving ≥ 1 $\log_{10}$ reduction from baseline in viral load at Week 24. Other subanalyses evaluated the mean viral load decrease and the proportion of patients with viral load < 50 copies/mL. This study also evaluated specific protease mutations and the relationship between them and darunavir response. **Data Analysis** Multivariate analysis was performed on efficacy data (intent-to-treat, time to loss of virologic response analysis) for the effects of baseline darunavir fold change, presence of susceptible control protease inhibitors, number of antiretroviral drugs (0, 1, ≥2) in the OBR, number of primary protease inhibitor mutations, and viral load (< 20,000, 20,000 to 100,000, > 100,000 copies/mL).
Criteria	**Inclusion criteria** Male and female subjects were included in the study if they were 18 years of age or older who had received at least three classes of antiretrovirals. Included subjects had been receiving a stable protease inhibitor-containing regimen for at least eight weeks prior to screening. Their plasma HIV-1 RNA had to be > 1,000 copies/mL. They also had to have at least one primary protease inhibitor mutation at screening, and have no CD4 cell count restrictions. **Exclusion criteria** Not reported
Results	**Primary Subanalysis:** *Proportion of patients achieving ≥ 1 $\log_{10}$ reduction from baseline in viral load at Week 24:* • Darunavir/ritonavir 600mg/100mg BID: 70% • Control: • Susceptible: 32% • Resistant: 16% • Overall: 21% **Other Subanalyses:** *Mean viral load decrease ($\log_{10}$ copies/mL):* • Darunavir/ritonavir 600mg/100mg BID: -1.89 • Control: • Susceptible: -0.58 • Resistant: -0.43 • Overall: -0.48 *Proportion of patients with viral load < 50 copies/mL:* • Darunavir/ritonavir 600mg/100mg BID: 45% • Control: • Susceptible: 24% • Resistant: 7% • Overall: 12% *Protease Mutations:* *% of darunavir patients achieving viral load < 50 copies/mL:* • If < 10 BL mutations: > 33% • If ≥ 10 BL mutations: ≤ 33% *Associated with lower darunavir response when present at BL (and associated with a greater number of*

	mutations): • V32I / L33F / I47V • I54L / L89V • V11I / I50V / I54M • G73S / L76V / I84V *Mutations not present at BL that developed in > 10% of virologic failures:* • V32I / L33F / I47V • I54L / L89V • I15V / M46I
Conclusions	Darunavir/ritonavir had significant efficacy compared with the control group, including those susceptible to their control protease inhibitor at baseline. Subjects with ≥ 10 baseline protease inhibitor resistance-associated mutations had decreased darunavir/ritonavir response; however, the response to darunavir/ritonavir was still greater than that of the control protease inhibitor. There were eleven specific mutations at baseline that were associated with a decrease in response to darunavir/ritonavir and with a greater number of mutations. The darunavir/ritonavir response rate in this population was still great than that of the control protease inhibitor. Mutations V32I, L33F, 147V, 154L, and L89V developed in at least 10% of virologic failures.

Citation	Data on file, Tibotec Therapeutics. (POWER 3 trial: safety and efficacy for the approved dose of darunavir/ritonavir 600mg/100mg BID in treatment-experienced HIV patients)
Study Goals	To provide additional safety and efficacy information for the approved dose of darunavir/ritonavir 600mg/100mg twice daily in treatment-experienced patients.
Methods	**Study Design** This study was an analysis of two non-randomized, open-label trials (POWER 3: TMC114-C208/TMC114-C215). The primary endpoint was the proportion of patients achieving ≥ 1 $\log_{10}$ reduction in HIV RNA by week 24. Other analyses included change in CD4 count and the impact of baseline characteristics (darunavir fold change (FC), CD4 count, number of primary protease inhibitor mutations, number of susceptible nucleoside reverse transcriptase inhibitors (NRTIs), in the OBR, use of the fusion inhibitor enfuvirtide, and prior use of tipranavir) on treatment response (achieving reduction of HIV RNA to < 50 copies/mL. Safety data included clinical and laboratory adverse events graded by their severity and relation to darunavir. **Data Analysis** Outcome and safety parameters were evaluated at baseline, week 2, week 4, and then every 4 weeks through week 24. CD4 counts were not determined at week 24. The intent-to-treat (ITT) population was assessed for time to loss of virologic response (TLOVR).
Criteria	**Inclusion criteria** Male and female patients were included in the study if their plasma HIV RNA was > 1000 copies/mL, had received at least 3 months of prior NRTI treatment, had received at least one NNRTI used in a failing regimen, had been treated with at least one PI for at least three months, had been receiving stable PI treatment for at least 8 weeks prior to screening, and had at least 1 PI mutation from the International AIDS Society USA 2004 list of 17 primary PI mutations. **Exclusion criteria** Patients were excluded from the study if they had any prior darunavir treatment.
Results	**Primary Endpoint:** *Proportion of patients achieving ≥ 1 $\log_{10}$ reduction from baseline in viral load at Week 24:* • Darunavir/ritonavir 600mg/100mg BID: 65% **Other Endpoints:** *Mean HIV RNA reduction from baseline to Week 24:* • Darunavir/ritonavir 600mg/100mg BID: -1.65 $\log_{10}$ copies/mL *Percentage of patients achieving undetectability (< 50 copies/mL)* • Darunavir/ritonavir 600mg/100mg BID: 40% *Mean CD4 count increase from baseline to week 20:* • Darunavir/ritonavir 600mg/100mg BID: 80 cells/µL *Percentage of patients achieving VL < 50 copies/mL* • 0 susceptible NRTIs in OBR: 29% • 1 susceptible NRTI in OBR: 48% • 2 susceptible NRTIs in OBR: 41% • Darunavir FC ≤ 10: 50% • Darunavir FC > 10: 13% • Patients using enfuvirtide for the first time: 45% • Patients using enfuvirtide non-naively: 27% • Patients not using enfuvirtide: 42%
Conclusions	The authors concluded that the data collected in the POWER 3 trial confirmed and supported the observations from POWER 1 and POWER 2 that included the same darunavir/ritonavir regimen. They also concluded that the number of primary PI mutations was poorly correlated with virologic response to darunavir/ritonavir.

Acquisition Costs

Drug	Dose	Cost/Day/patient ($)	Cost/Year/patient ($)
Darunavir + Ritonavir	600mg + 100mg BID	21.00	7,665.00
Indinavir	800mg Q 8 hours	11.16	4,073.40
Saquinavir + Ritonavir	400mg + 400mg BID	15.08	5,504.20
Lopinavir/ritonavir	800/200mg QD	15.12	5,518.80
Lopinavir/ritonavir	400/100mg BID	15.12	5,518.80
Fosamprenavir	1400mg BID	25.76	9,402.40
Fosamprenavir + Ritonavir	1400mg + 200mg QD	15.16	5,533.40
Atazanavir	400mg QD	17.12	6,248.80
Atazanavir + Ritonavir	300mg + 100mg QD	18.00	6,570.00
Nelfinavir	1250 BID	14.92	5,445.80
Tipranavir + Ritonavir	500mg + 200mg BID	23.84	8,701.60
Enfuvirtide	90mg SC BID	42.72	15,592.80

Cost Analysis

There are no published pharmacoeconomic analyses.

Conclusions

Darunavir is a new HIV-1 protease inhibitor that selectively inhibits the cleavage of HIV encoded Gag-Pol polyproteins in virus infected cells. This results in the prevention of the formation of mature virus particles. Darunavir is indicated for the treatment of HIV infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one protease inhibitor. The recommended dosing regimen is 600mg administered with 100mg of ritonavir twice daily with food. Results from Phase IIb and Phase III clinical trials showed superiority of darunavir/ritonavir versus other protease inhibitors. All response parameters in the POWER 1 and POWER 2 individual analyses were significantly better ($p < 0.001$) for darunavir/ritonavir when compared with patients receiving an investigator-selected protease inhibitors in the control arm. Superior efficacy or darunavir/ritonavir was demonstrated in achieving the primary endpoint of proportion of patients with a ≥ 1 $\log_{10}$ reduction in viral load from baseline at week 24, proportion of patients with undetectable viral loads, and CD4 cell count increases. Darunavir response rates in Phase IIb studies POWER 1 and POWER 2 were affected by both specific mutations and the number of baseline mutations. The presence of baseline mutations V32I, I47V, or I54L or M, was associated with decreased susceptibility and decreased virologic response to darunavir. The safety profile of darunavir is similar to that of other protease inhibitors. Darunavir may be most advantageous when combined with other active antiretroviral agents and used in patients with known protease inhibitor mutations and few or no remaining treatment options. In respect to cost, darunavir is comparable to other recently approved protease inhibitors.

Recommendations

Darunavir should only be used in heavily treatment-experienced HIV patients. Because darunavir may provide a treatment benefit over existing antiretroviral options based on its activity against clinical isolates resistant to multiple protease inhibitors, darunavir should be considered for formulary status with restrictions to infectious disease specialists to ensure appropriate use.

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9. Data on file, Tibotec Therapeutics. (Multivariate pooled analysis of potential prognostic factors from week 24 efficacy data from POWER 1 and POWER 2 trials).
10. Data on file, Tibotec Therapeutics. (POWER 3 trial: safety and efficacy for the approved dose of darunavir/ritonavir 600mg/100mg BID in treatment-experienced HIV patients).

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