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REVIEW

Managing treatment-experienced pediatric and adolescent HIV patients: role of darunavir

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Abstract: Darunavir is currently the most recently approved HIV-1 protease inhibitor. It is approved for twice-daily dosing with ritonavir in treatment-experienced patients as young as 6 years of age and is available in numerous pill strengths. Emergence of darunavir-specific mutations is generally slow; therefore it can retain activity against viral strains that are resistant to other protease inhibitors, including tipranavir. Darunavir pharmacokinetics, clinical efficacy, resistance mutations and pharmacodynamics, and adverse effects are reviewed here. Substantial data support its use as a potent, well-tolerated option for salvage therapy in highly treatment-experienced children and adolescents.

Keywords: darunavir, protease inhibitors, treatment, child, adolescent

Introduction

As of 2007, 2 million children under 15 years of age were living with HIV in the world, with approximately 370,000 new infections and 270,000 deaths that year.[1] Of the 2.3 million new adult infections in 2007, 45% (over 1 million) were in adolescents aged 15 to 24 years of age. In some developing countries, seroprevalence of HIV among adolescent males is higher than 5%, with females 2 to 4 times higher still, reflecting the burden of the epidemic borne by girls and women.

Nonetheless, in countries that have the resources and infrastructure to ensure consistent access to combination antiretroviral therapy, the trajectory of the epidemic has been dramatically altered. For example, in North America, the seroprevalence rate among adults was only 0.6% in 2007, and there were estimated to be just 4400 children living with HIV infection, with fewer than 500 new infections that year in those under 15 years of age.[1] Despite the low burden of HIV infection in developed countries relative to the developing world, the most treatment-experienced children and adolescents presently reside and obtain care in regions of the world such as the United States (US) and Europe. As therapy is increasingly available worldwide, however, the number of treatment-experienced children will correspondingly rise globally. For these young patients, there is and will be a chronic and pressing need for drugs that are active against HIV strains which are resistant to multiple antiretroviral agents.[2]

Control of HIV infection is accomplished through the use of combination antiretroviral therapy.[3] There are now six therapeutic classes of medications available, as shown in Table 1, although not all are licensed for use in children. Entry inhibitors include CCR5 antagonists and fusion inhibitors. The former bind to the human

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Table 1 Current lower age of FDA-licensure for antiretroviral drugs obtained from package inserts

Drug	Lower age for licensed prescribing
Nucleoside reverse transcriptase inhibitors	
Abacavir (Ziagen®)	3 months
Didanosine (Videx®, Videx EC®)	6 months, 6 years
Emtricitabine (Emtriva™)	3 months
Lamivudine (Epivir®)	3 months
Stavudine (Zerit®)	6 months
Tenofovir disoproxil fumarate (Viread®)	18 years
Zidovudine (Retrovir®)	6 weeks (treatment dosing) birth (prophylactic dosing)
Nonnucleoside reverse transcriptase inhibitors	
Efavirenz (Sustiva™)	3 years
Etravirine (Intelence™)	16 years
Nevirapine (Viramune®)	15 days
Combination NRTI and/or NNRTI	
Abacavir + lamivudine (Epzicom®)	16 years
Abacavir + lamivudine + zidovudine (Trizivir®)	Variable (>40 kg)
Tenfovir + emtricitabine (Truvada®)	18 years
Tenfovir + emtricitabine + Efavirenz (Atripla®)	18 years
Zidovudine + lamivudine (Combivir®)	12 years
Protease inhibitors (PI)	
Atazanavir (Reyataz™)	6 years
Darunavir (Prezista®)	6 years
Fos-amprenavir (Lexiva™)	2 years
Indinavir (Crixivan®)	18 years
Lopinavir/ritonavir (Kaletra®)	14 days
Nelfinavir (Viracept®)	2 years
Ritonavir (Norvir®)	2 years (treatment); variable as boosting agent with other PIs
Saquinavir (Invirase®)	16 years
Tipranavir (Aptivus®)	2 years
Entry and fusion inhibitors	
Enfuvirtide (Fuzeon™)	6 years
Maraviroc (Selzentry®)	16 years
Integrase inhibitor	
Raltegravir (Isentress®)	16 years

membrane receptor CCR5 to prevent binding of virions to susceptible cells. They are the only therapeutic agents with a human target. Fusion inhibitors disrupt the process by which virions inject their contents into the target cell cytoplasm by binding to the viral gp41 protein, which is essential to the process. Nucleoside reverse transcriptase inhibitors (NRTIs) are analogues of nucleosides/tides (eg, adenine, guanine, cytosine, thiamine) and are competitive antagonists of the reverse transcription step from viral RNA to double-stranded DNA. Non-NRTIs (NNRTIs) similarly inhibit this step, but through a noncompetitive antagonism. Integrase inhibitors prevent the insertion of proviral DNA into the host cell genome. Finally, protease inhibitors (PIs) stop cleavage and activation of the viral *gag-pol* polyprotein by the viral protease.

The first PI licensed for adults by the US Food and Drug Administration (FDA) in December 1995 was saquinavir (Invirase®), ushering in the era of effective combination therapy for HIV. Saquinavir was followed shortly thereafter by ritonavir (Norivr®) and indinavir (Crixivan®) in March 1996. There have since been 8 additional PIs brought to market, many with overlapping resistance profiles. In this article we review darunavir (Prezista™, Tibotec Pharmaceuticals), currently the most recently licensed PI. We will consider the activity of darunavir against HIV strains resistant to many or all other PIs and its role in the management of HIV-infected children and adolescents.

Darunavir description and approval history

Darunavir is a nonpeptidic inhibitor of HIV-1 and HIV-2 protease, and like other PIs, it prevents cleavage of the HIV polyprotein encoded by the *gag-pol* region. Darunavir, and its structural analogue, amprenavir, both bind to a unique site on the wild-type protease enzyme at a rate approximately one order of magnitude faster than other protease inhibitors, including tipranavir.[4] Furthermore, darunavir disassociates from the wild type protease at a rate >1000-fold more slowly than that of other protease inhibitors, including amprenavir and tipranavir. Together, darunavir's rapid binding and slow disassociation confer a binding strength two orders of magnitude higher than any other protease inhibitor, which is believed to confer potency even against viral strains resistant to other PIs.[4–6]

Darunavir is one of 28 unique or combined-formulation antiretroviral drugs currently licensed by the FDA and available for use by HIV-infected adults. Of these medications, 19 (68%) are also licensed for use in HIV-infected children and adolescents, defined by the US Code of Federal Regulations[7] as less than 16 years of age, although the lower age limit for licensed dosing varies by drug, as shown in Table 1. Among the agents from new therapeutic classes (maraviroc and raltegravir) or the "second-generation" agents in older

classes (darunavir, tipranavir, and etravirine), only darunavir and tipranavir are FDA-licensed for children and adolescents. Darunavir was originally licensed on June 23, 2006, and the label was modified to include children on December 18, 2008. In the US it is approved for the treatment of HIV-1 infection in treatment-naïve and treatment-experienced adults and treatment-experienced children over 6 years of age. It is not currently licensed for children in Europe, although application has been submitted for licensure as young as 3 years of age.

Pharmacokinetics

Although the majority of pharmacokinetic information for darunavir has been obtained from adults, DELPHI (Darunavir EvaLuation in Pediatric HIV-1-Infected treatment-experienced patients, TMC 114-C212) was an open-label, Phase I/II manufacturer-sponsored investigation to determine the pharmacokinetics, safety, and efficacy of darunavir in children and adolescents.[8–10] After 2 weeks of dosing, darunavir plasma concentrations were measured to obtain pharmacokinetic, safety and efficacy data from 44 children. Pharmacokinetic results from DELPHI and from adult studies are summarized in Table 2. With the goal of best matching adult darunavir exposures measured after dosing with darunavir 600 mg plus ritonavir 100 mg twice daily, the final pediatric dosing recommendations, shown in Table 3, were selected for the 48-week safety and efficacy Part II of the DELPHI study (discussed in the Clinical Experience section). These are the same weight-based recommendations as those included in the FDA-approved package insert.

Food, while slowing the rate of darunavir absorption[11] also increases the overall bioavailability by 30% relative to the fasted state, and thus the drug should be given with food; however, meal composition is irrelevant.[11,12] Metabolism is almost exclusively by cytochrome P450 (CYP) 3A4;[12] therefore, darunavir is to be administered with low-dose ritonavir, which is a potent CYP3A4 inhibitor[12] and raises the concentrations of darunavir significantly. Approximately 80% of darunavir is eliminated in the feces, half of which is unchanged parent compound when given with ritonavir.[13]

On October 21, 2008, the FDA licensed an amended once-daily dosing regimen for darunavir in treatment-naïve HIV-infected adults. In this population the approved daily dose is 800 mg in combination with ritonavir 100 mg. Darunavir at this dose was studied as one of several darunavir dosing arms vs comparator protease inhibitors in the POWER-1 and -2 (Performance Of TMC114/r When evaluated in treatment-Experienced patients with PI Resistance) studies[14] and as the only darunavir treatment arm vs once or twice daily lopinavir/ritonavir in the ARTEMIS trial

Table 2 Pharmacokinetics of darunavir in children and adults from the US Package Insert[12] and other references as noted

Observation or parameter (adult patients)		
Protein binding	95%	
Bioavailability, absolute		
without ritonavir	37%	
with ritonavir	82%	
Bioavailability, relative		
food[11]	+30%	
T_{max}[a], hours	2.5–4.0	
Terminal half-life, hours	15 (when co-administered with ritonavir)	
Clearance, L/h (intravenous dosing with ritonavir)	5.9	
Volume of distribution, L (intravenous dosing)[51]	131	
Effect of hepatic impairment	No significant change with moderate impairment (Child-Pugh Class B)	
Effect of renal impairment	No significant change with moderate impairment (creatinine clearance 30–60 mL/min)	
Typical darunavir	Pooled POWER 1 and 2	DELPHI
concentrations[b]	N = 119 adults	N = 74 children
AUC_{0-24}, μg·h/mL[c] median (range)	123.3 (67.7–213.0)	127.3 (67.1–230.7)
C_{0h}, μg/mL[d] median (range)	3.5 (1.3–7.4)	3.9 (1.8–7.8)

[a]Time to maximum concentration
[b]Observed after darunavir 600 mg plus ritonavir 100 mg twice daily in adults, and according to dosing in Table 2 in children.
[c]Area under the time-concentration curve from 0 to 24 hours, calculated as 2*AUC_{0-12}.
[d]Concentration immediately prior to dosing, ie. trough concentration.

Table 3 FDA-licensed darunavir/ritonavir dosing in children and adolescents

Weight		Dose	
(kg)	(lbs)	(darunavir mg)	(ritonavir mg)
20 to <30	44 to <66	375	50
30 to <40	66 to <88	450	60
≥40	≥88	600	100

(AntiRetroviral Therapy with TMC114 ExaMined In naïve Subjects).[15] With once-daily dosing in adults, the AUC of 87.9 mg·h/L and C_0 of 2.0 mg/L[12] are 71% and 57% of the twice-daily adult dose.[12] However, there is no experience with once-daily dosing of darunavir in children or adolescents, and it is not recommended.[12]

In the US, darunavir is supplied as film-coated tablets in strengths of 75, 300, 400, and 600 mg, which are stable at room temperature. There is a nonlicensed liquid formulation which has been used in clinical research only.

In summary, darunavir is available in numerous dosage strengths which make weight-based dosing in children feasible, although a liquid formulation is not currently on the market. The drug is approved for use in children as young as six years of age and the dosing recommendations in Table 3 approximate the exposures seen in adults who are given 600 mg in combination with ritonavir 100 mg, both twice daily. Once daily dosing has not been studied in children and is not currently recommended.

Drug interactions

Darunavir itself is both a substrate and inhibitor of CYP3A4,[12] and is always co-administered with ritonavir. Ritonavir interacts with several drug metabolizing enzymes in complex and opposing ways. It is a potent inhibitor of CYP3A4, and a lesser inhibitor of CYP2D6.[12] On the other hand, it is an inducer of several cytochromes P450, including 1A2, 2B6, 2C9, and 2C19, as well as glucuronyl transferase.[16] Therefore, there is significant potential for drug–drug interactions. In general, concomitant medications which are primarily metabolized by CYP3A4 or 2D6 will tend to have increased concentrations, due to inhibition of these enzymes by the combination of darunavir and ritonavir, while medications metabolized by other CYP isoforms will have lowered concentrations due to induction of metabolism by ritonavir.[12] Darunavir has been studied in combination with other antiretroviral agents and many nonantiretroviral drugs, all of which are reported in the package insert[12] and summarized in Table 4. A useful, continuously updated resource for interactions involving antiretroviral agents is the HIV Drug Interaction website (http://www.hiv-druginteractions.org), maintained by the University of Liverpool.

The most significant interactions with other antiretrovirals to avoid are lopinavir and saquinavir which lower darunavir concentrations. Both darunavir and indinavir concentrations are somewhat raised with coadministration, so this combination should only be used with caution. Atazanavir, efavirenz, etravirine, nevirapine, and tenofovir disoproxil fumarate have all been shown to lack a significant interaction with darunavir.

Clinical efficacy

Major clinical trials to establish the efficacy and safety of darunavir in patients are summarized in Table 5. Efficacy will be discussed here, while safety and tolerability will be discussed separately. Published clinical experience with darunavir in children and adolescents is limited to a case report of successful darunavir-based salvage therapy in a single child with multi-drug resistant, perinatally transmitted HIV[17] and abstracts/posters from the DELPHI study of 80 PI-experienced children ages 6–17 years with baseline viral loads >1000 copies/mL, who received 48 weeks of darunavir plus ritonavir plus optimized background therapy.[8,10] Baseline characteristics of the DELPHI study population are shown in Table 6. At 48 weeks, the percent of children with ≥1 $\log_{10}$ drop in viral load from baseline was 65% and the percent with <50 copies/mL was 48%. In accordance with FDA guidelines, analysis was by intent to treat, time to loss of virologic control (ITT-TLOVR), where success for a given virologic endpoint is defined only in those who did not withdraw, whose regimen was not switched for virologic failure, and who had reached the endpoint on two consecutive visits, with no subsequent failure before end of study.[18] All others are considered failures. The mean change in CD4+ cell count was +147 cells/mm,[3] with analysis by ITT-noncompleter equals failure (ITT-NC = F), where missing data from individuals due to premature study termination or missed visits are replaced with baseline values.

These response and adverse effect rates are comparable to those observed in adults in the POWER studies.[19] POWER 1 and 2 were Phase IIB studies in different geographic regions, which compared the safety and efficacy of darunavir/ritonavir (600/100 mg twice daily) or placebo plus an optimized background antiretroviral regimen in highly treatment-experienced adults, similar to the children and adolescents in DELPHI. POWER 3 was an extension of POWER 1 and 2 in order to satisfy regulatory requirements;

Table 4 Significant drug interactions and recommendations with darunavir/ritonavir (DRV/r)

Drug	Effect on drug	Effect on darunavir	Recommendation
HIV-nucleoside reverse transcriptase inhibitors (NRTIs)			
didanosine	↔didanosine	↔darunavir	Didanosine should be administered one hour before or two hours after DRV/r (which are administered with food).
tenofovir disoproxil fumarate	↔tenofovir disoproxil fumarate	↔darunavir	No dosage adjustments are required with tenofovir disoproxil fumarate.
HIV-nonnucleoside reverse transcriptase inhibitors (NNRTIs)			
efavirenz[52]	↑efavirenz	↓darunavir	Changes in concentrations are not judged to be clinically significant and no dosage adjustment is recommended.
etravirine	↓etravirine	↔darunavir	
nevirapine	↑nevirapine	↑darunavir	
HIV-protease inhibitors (PIs)			
indinavir	↑indinavir	↑darunavir	The appropriate dose of indinavir, lopinavir or saquinavir in combination with DRV/r has not been established; hence, co-administration is not recommended.
lopinavir/ritonavir	↔lopinavir	↓darunavir	
saquinavir[53]	↔saquinavir	↓darunavir	
atazanavir[54]	↔atazanavir	↔darunavir	No significant interaction exists with atazanavir and no dosage adjustment is recommended.
Antacids			
omeprazole[55]	↔omeprazole	↔darunavir	No dose adjustments are required.
ranitidine[55]	↔ranitidine		
Antiarrhythmics			
bepridil	↑antiarrhythmics		Caution is warranted; monitor concentrations of antiarrhythmics when co-administered with DRV/r. The lowest dose of digoxin should initially be prescribed. The serum digoxin concentrations should be monitored and used for titration of digoxin dose to obtain the desired clinical effect.
lidocaine (systemic)	↑digoxin		
quinidine			
amiodarone			
flecainide			
propafenone			
digoxin			
Anticoagulant			
warfarin	↓warfarin	↔darunavir	Monitor international normalized ratio (INR)
Anticonvulsants			
carbamazepine	↑carbamazepine	↔darunavir	No dose adjustments when initiating therapy. Monitor anticonvulsant concentrations and clinical response, with dose titration to achieve desired response.
phenobarbital,	↓phenytoin		
phenytoin	↓phenobarbital		
Antidepressants			
trazodone	↑trazodone	ND	Use with caution and consider a lower dose of trazodone or desipramine.
desipramine	↑desipramine		

(*Continued*)

Table 4 (*Continued*)

Drug	Effect on drug	Effect on darunavir	Recommendation
Antibacterial			
clarithromycin[56]	↑clarithromycin	↔darunavir	No dose adjustment of the combination is required for patients with normal renal function. For patients with renal impairment, the following dose adjustments should be considered: • For subjects with creatinine clearance of 30–60 mL/min, the dose of clarithromycin should be reduced by 50%. • For subjects with creatinine clearance of <30 mL/min, the dose of clarithromycin should be reduced by 75%.
Antifungals			
ketoconazole[57] itraconazole voriconazole	↑ketoconazole ↑darunavir ↑itraconazole (not studied) ↓voriconazole (not studied)	↑darunavir (ketoconazole or itraconazole)	When co-administration is required, the daily dose of ketoconazole or itraconazole should not exceed 200 mg. Voriconazole should not be administered to patients receiving darunavir/ritonavir unless an assessment of the benefit/risk ratio justifies the use of voriconazole.
Antimycobacterial			
rifabutin	↑rifabutin ↑25-*O*-desacetylrifabutin	↑darunavir	Reduce dose of rifabutin by at least 75% of the usual dose (300 mg once daily) to a maximum dose of 150 mg every other day. Increased monitoring for adverse events is warranted in patients receiving this combination and further dose reduction of rifabutin may be necessary.
rifampin	ND	↓darunavir	Rifampin is a potent inducer of CYP450 metabolism. DRV/r should not be used in combination with rifampin, as this may cause significant loss of therapeutic effect to DRV/r. This combination is **CONTRAINDICATED**.
β-Blockers			
metoprolol timolol	↑beta-blockers	ND	Caution is warranted and clinical monitoring of patients is recommended. A dose decrease may be needed for these drugs.
Benzodiazepines			
midazolam triazolam	↑midazolam ↑triazolam	ND	Co-administer in a setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Consider dosage reduction for midazolam, especially if more than a single dose of midazolam is administered. Co-administration of oral midazolam or triazolam is **CONTRAINDICATED**.

Calcium channel blockers			
felodipine nifedipine nicardipine	↑calcium channel blockers	ND	Use caution and clinical monitor patients for clinical effect.
Corticosteroid: systemic			
dexamethasone	ND	↓darunavir	Chronic, systemic dexamethasone induces CYP3A and can thereby decrease darunavir plasma concentrations.
Corticosteroid: inhaled/nasal			
fluticasone propionate	↑fluticasone propionate (plasma)	ND	Consider alternatives, particularly for long term use.
Ergot derivatives			
dihydroergotamine ergonovine ergotamine methylergonovine	↑ergots	ND	Potential for serious and/or life-threatening events such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues. Combination with DRV/r is **CONTRAINDICATED**.
GI motility agent			
cisapride	↑cisapride	ND	There is a potential for serious and/or life-threatening reactions such as cardiac arrhythmias. This combination is **CONTRAINDICATED**.
Herbal product			
St. John's Wort	ND	↓darunavir	DRV/r therapeutic efficacy may be compromised. This combination is **CONTRAINDICATED**.
HMG-CoA reductase inhibitors			
pravastatin atorvastatin rosuvastatin lovastatin simvastatin	↑pravastatin ↑atorvastatin ↑rosuvastatin ↑lovastatin ↑simvastatin	ND	Use the lowest possible dose of atorvastatin, pravastatin or rosuvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as fluvastatin. Use of lovastatin or simvastatin with DRV/r is **CONTRAINDICATED** due to potential for myopathy, including rhabdomyolysis.
Immunosuppressants			
cyclosporine tacrolimus sirolimus	↑immunosuppressants	ND	Monitor concentrations of the immunosuppressive agent.
Narcotic analgesic			
methadone	↓methadone	ND	No initial adjustment of methadone dosage is required; however, monitor clinical effect as the dose of methadone during maintenance therapy may need to be adjusted in some patients.

(*Continued*)

Table 4 (*Continued*)

Drug	Effect on drug	Effect on darunavir	Recommendation
Neuroleptics risperidone thioridazine pimozide	↑neuroleptics	ND	There is no recommended initial dose adjustment for risperidone or thioridazine, but monitor clinical effect closely: a dose decrease may be needed for these drugs. Co-administration of pimozide and DRV/r is **CONTRAINDICATED** due to risk of potential for serious/life-threatening reactions such as cardiac arrhythmias.
Oral contraceptives/estrogen ethinyl estradiol[58] norethindrone	↓ethinyl estradiol ↓norethindrone	ND	Consider alternative methods of nonhormonal contraception.
PDE-5 inhibitors sildenafil[59] vardenafil tadalafil	↑PDE-5 inhibitors	ND	Sildenafil at a single dose not exceeding 25 mg in 48 hours, vardenafil at a single dose not exceeding 2.5 mg dose in 72 hours, or tadalafil at a single dose not exceeding 10 mg dose in 72 hours can be used with increased monitoring for PDE-5 inhibitor-associated adverse events.
Selective serotonin reuptake inhibitors (SSRIs) sertraline paroxetine	↓sertraline ↓paroxetine	↔darunavir	Titrate dose carefully based on a clinical assessment of antidepressant response. In addition, patients on a stable dose of sertraline or paroxetine who start treatment with DRV/rtv should be monitored for antidepressant response.

Notes: ↔, No change; ↑, Increase; ↓, Decrease; ND, No data. All data are from the Prezista® package insert,[12] unless otherwise indicated.

however, a placebo arm was not included in POWER 3.[20] At week 48, combined analysis of 230 participants from POWER 1 and 2 showed a drop of ≥1 $\log_{10}$ viral copies/mL from baseline in 61% of the participants, and 45% of them achieved <50 copies/mL[19] (compared with 65% and 48% of the DELPHI participants). In addition to baseline PI mutations and RAMs, the number of active NRTIs in the background regimen was strongly associated with ≥1 $\log_{10}$ drop in viral copies/mL: 42% in the darunavir arm vs none in the comparator arm reached this endpoint with no active NRTIs ($P < 0.0001$); with one active NRTI it was 69% and 13% ($P < 0.0001$); and with ≥2 active NRTIs, it was 68% and 28% ($P = 0.001$). The mean CD4+ cell increase in POWER 1 and 2 was 102 cells/mm^3 (compared with 147 in the children and adolescents in the DELPHI cohort). Virologic and immunologic results were very similar from the additional patients in POWER 3, as shown in Table 5.[20]

Not surprisingly, given the structural similarity to amprenavir, a previous history of failure with fos-amprenavir was associated with reduced response to darunavir.[21] In the POWER and DUET studies, average 48-week viral load change from baseline was –1.47 $\log_{10}$ (± 0.15) copies/mL in 73 patients with a history of failure on an amprenavir-based regimen vs –1.65 $\log_{10}$ (± 0.06) copies/mL in 450 patients regardless of prior amprenavir exposure ($P < 0.0001$, T-Test).[22] Although this was highly statistically significant, it has been argued that the clinical significance of a 0.3 $\log_{10}$ difference is minimal[23] and the percentage of those achieving <50 copies/mL in each group at 48 weeks was not significantly different (38% vs 45%, $P = 0.40$, Chi-square).

ARTEMIS was a Phase III, randomized, open-label, noninferiority comparison of either darunavir/ritonavir (800/100 mg once daily) or lopinavir/ritonavir plus optimized background antiretrovirals in treatment-naïve adults.[15] Therefore, the ARTEMIS study population was different than the DELPHI and POWER populations by prior treatment experience. Accordingly, virologic response rates were higher in ARTEMIS, with 84% of 343 participants in the darunavir arm achieving <50 copies/mL at week 48, which was not inferior to the lopinavir arm (78% of 346). The median changes in CD4+ cell count at week 48 were +137 and +141 cells/mm^3 for darunavir and lopinavir, respectively.

TITAN (TMC114/r In Treatment-experienced pAtients Naïve to lopinavir) was a Phase III, randomized, open label companion trial to ARTEMIS, which again compared darunavir to lopinavir, but in a treatment-experienced population who were naïve to lopinavir, although participants did not have to be susceptible to lopinavir at baseline.[24] Participants were randomized 1:1 to either darunavir/ritonavir 600/100 mg twice daily, or lopinavir/ritonavir 400/100 mg twice daily. Both study arms included optimized background therapy, but enfuvirtide was excluded. At 48 weeks, 71% of the patients in the darunavir arm had <50 viral copies/mL by ITT-TLOVR analysis, vs 60% in the lopinavir arm ($P = 0.005$). Similarly, the mean change in viral load from baseline was –1.95 vs –1.72 $\log_{10}$ copies/mL in the darunavir and lopinavir arms, respectively ($P = 0.046$). Among patients with baseline reduced susceptibility to lopinavir, the percentage in each group with <50 viral copies/mL was 72% vs 28%, highlighting the usefulness of darunavir in the setting of baseline lopinavir resistance. The mean change in CD4+ cells was not significantly different in the two arms: +88 vs +81 cells/μL.

In summary, darunavir has demonstrated virologic and immunologic efficacy in highly treatment-experienced children and adolescents which closely matches the efficacy in treatment-experienced adults. Darunavir has not been studied in treatment-naïve children and adolescents, but is effective in treatment-naïve adults. Prior failure with amprenavir or fos-amprenavir may be associated with slightly reduced efficacy, due to structural similarities between amprenavir and darunavir.

Pharmacokinetic–pharmacodynamic predictors of darunavir clinical efficacy

Numerous pharmacokinetic and pharmacodynamic factors have been studied to predict virologic and immunologic responses to darunavir therapy, including baseline darunavir susceptibility, darunavir drug concentrations, total number of active drugs in the regimen, and inhibitory quotients. These are summarized in Table 7 and detailed in the following sections.

Susceptibility of HIV isolates to antiretroviral agents at baseline prior to starting new therapy or at the time of therapeutic failure may be broadly measured using one of two techniques: phenotypic or genotypic, with a third technique a hybrid of the two known as a virtual phenotype.[25] Phenotypic susceptibility is reported as the concentration of drug required to inhibit laboratory growth of the patient's dominant viral strains by 50% (IC_{50}), or as the fold-change in IC_{50} relative to the IC_{50} for wild-type virus. A related but not equal parameter is the concentration required for 50% of maximal in vivo or clinical effect (EC_{50}), which is a benchmark defined through clinical testing: against wild-type virus, the protein-corrected

Table 5 Summary of darunavir clinical trials

	DELPHI	POWER 1, 2	POWER 3	ARTEMIS	TITAN
N (Darunavir)	80	131	327	343	298
Study design	Phase II	Phase IIb	Phase II	Phase III	Phase III
Time of analysis	48 weeks	48 weeks	24 weeks	48 weeks	48 weeks
Population	Pediatric	Adult	Adult	Adult	Adult
Treatment history	Highly experienced	Highly experienced	Highly experienced	Naïve	Experienced, LPV-naïve
Darunavir/ritonavir (DRV/r) Dose (mg)	All doses are bid 20 to <30 kg: 375/50 30 to <40 kg: 450/60 ≥40 kg: 600/100	400/100 daily, 800/100 daily, 400/100 bid, or 600/100 bid[a]	600/100 bid	800/100 daily	600/100 bid
Comparator (Comp)	None	Optimized PI-based	None	LPV/r 400/100 bid or 800/200 daily	LPV/r 400/100 bid
Viral load (VL) <50 copies/mL (DRV/ Comp)	48%	45%/10%	40%	84%/78%	71%/60%
Mean $\Delta\log_{10}$ (DRV/Comp)	NR	−1.63/−0.35	−1.65	NR	−1.95/−1.72
>1 $\log_{10}$ drop copies/mL (DRV/Comp)	65%	61%/15%	65%	NR	77%/69%
Mean ΔCD4+ cells/mm^3 (DRV/Comp)	+147	+102/+19	+80	+137/+141	+88/+81
Major DRV adverse events	Diarrhea (n = 1) Rash (n = 1)	Nausea (18%) Nasopharyngitis (14%) Upper respiratory infection (12%) Herpes simplex (12%)	Nausea (10%) Diarrhea (14%) Nasopharyngitis (11%)	Nausea (2%) Diarrhea (4%) Rash (3%)	Nausea (4%) Diarrhea (8%)
Major DRV laboratory abnormalities	Neutropenia (13%) ↑Lipase (11%) ↑Alanine amino transferase (6%) ↑Aspartate amino transferase (5%)	↑Triglycerides (15%) ↑Total cholesterol (7%) ↑Amylase (6%) ↑Lipase (5%)	↑ Amylase (7%) ↑ Lipase (3%) ↑ Partial thromboplastin time (3%) Leucopenia (7%) Lymphopenia (5%) Neutropenia (5%) ↑ Total cholesterol (4%) ↑ Triglycerides (6%) ↑ Aspartate amino transferase (2%) ↑ Alanine amino transferase (2%) ↑ Gamma glutamyl transferase (3%)	↑Triglycerides (3%) ↑Total cholesterol (13%) ↑Amylase (7%)	↑Total cholesterol (32%) ↑Low-density lipoprotein (19%) ↑Amylase (11%) ↑Lipase (5%)
Reference	8,10	19	20	15	24

[a]Only dose included in analysis.

Abbreviation: LPV, lopinavir; PI, protease inhibitor.

darunavir EC_{50} is 55 ng/mL.[15] Genotypic susceptibility is reported as a list of mutations in the patient's dominant viral strains, along with rules-based interpretations, ie,susceptible, possibly resistant, or resistant. The virtual phenotype provides an estimation of viral IC_{50} or fold-change in IC_{50}, and is calculated using the patient's genotype, a large database of paired viral genotype-phenotype measurements, and weighted linear regression techniques.[26]

Common measures to quantify concentration-effect relationships include comparisons of total drug exposure (AUC), trough drug concentrations, or inhibitory quotients (IQ) in virologic responders vs nonresponders. The IQ is calculated as the ratio of drug concentration to viral susceptibility to that drug.[27] Typically, the predose trough concentration is the reference drug concentration, while susceptibility may be quantified as the fold change in IC_{50} relative to wild-type virus by phenotypic or virtual phenotypic assays (pIQ, vIQ) or by the number of resistance associated mutations (RAMs) by genotypic assay (gIQ).

Table 6 Baseline characteristics of the DELPHI pediatric cohort

Demographics	n (%)
Male	57 (71)
Age	
6 to <12 years	24 (30)
12 to 17 years	56 (70)
Perinatal infection	62 (78)
CDC class C	40 (50)
Disease characteristics	
Mean (SD) viral load (log_{10} copies/mL)	4.64 (0.80)
Median (range) CD4+ cell count (cells/mm^3)	330 (6–1505)
Median (range) CD4+ cell %	17 (1–47)
Previous antiretroviral treatment	
Median (range) number of drugs	9 (3–19)
≥1 PI, n (%)	77 (96)
≥1 NNRTI, n (%)	63 (79)
≥2 NRTIs, n (%)	80 (100)
Enfuvirtide, n (%)	8 (10)
Baseline mutations	
PI, median (range) number per patient	11 (0–19)
Major PI, median (range) number per patient	3 (0–6)
Patients with darunavir RAMs, n	
0	39
1	17
2	15
≥3	9
NNRTI, median (range) number per patient	2 (0–4)
NRTI, median (range) number per patient	4 (0–8)

Abbreviations: CDC, Centers for Disease Control; NRTI, nucleoside reverse transcriptase inhibitors; NNRTI, non-nucleoside reverse transcriptase inhibitors; PI, protease inhibitors; RAMs, resistance associated mutations.

Genotypic susceptibility and outcomes

Combined analysis[28] from the POWER 1, 2 and 3 and DUET (etravirine plus placebo or darunavir in treatment-experienced patients) studies detected 11 darunavir Resistance Associated Mutations (RAMs) in 10 codons, which have been adopted in all three of the major HIV resistance databases (International AIDS Society-USA [IAS, http://www.iasusa.org], Stanford [http://hivdb.stanford.edu]., and French National Agency for AIDS Research [ANRS, http://www.hivfrenchresistance.org]). The mutations are V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V and L89V. Mutation overlap with other PIs according to IAS is shown in Table 8, although mutations for older drugs such as indinavir, nelfinavir and saquinavir are likely under-represented due to lack of current research.[29]

The Virco virtual phenotype database contains 82 unique mutations or pairs of mutations identified using their linear modeling algorithm which increase the fold-change in darunavir phenotypic IC_{50}, including all of the 11 darunavir-specific RAMs.[30] However, only four (I54L, T74P, L76V, and I84V) of these primary RAMs individually contribute more than a 2-fold increase in darunavir IC_{50} (Virco, Inc., data on file). However, there is a relative paucity of primary darunavir RAMs in PI-resistant clinical samples submitted to Virco,[28] suggesting that resistance to darunavir emerges slowly, and that darunavir can retain activity against viral quasispecies with a high degree of resistance to other PIs.

The number of darunavir RAMs present prior to therapy with darunavir is related to the degree of PI experience, and influences the success rate of darunavir therapy. In the combined POWER cohort, which was highly PI-experienced, there was a median of 12 PI RAMs prior to initiating therapy with darunavir. Among these PI RAMs, at least one was a darunavir RAM in 82% of patients , ranging up to 4 darunavir RAMs in 11% of the patients.[31] The most commonly observed darunavir RAMs were L33F (42%), I84V (39%), and I47V (13%), with others ranging between 5% and10%. The probability of achieving a viral load of <50 copies/mL ranged from 65% in those with no baseline darunavir RAMs, to only 10% in those with ≥4 RAMs. In the PREDZISTA cohort, 89% of those with <4 darunavir RAMs achieved <200 copies/mL at 12 weeks, vs none with >5 RAMs.[32]

Table 7 Significant pharmacokinetic and pharmacodynamic predictors of virologic response with darunavir-based therapy

Predictor	Outcome	Notes
Baseline virtual phenotypic susceptibility		
	VL < 50 copies/mL	POWER 1, 2, 3[31]
Susceptible (S)		
(IC_{50} FC < 10)	50%	
Partial susceptibility (P)		
(IC_{50} FC 10–40)	25%	
Resistant (R)		
(IC_{50} FC > 40)	13%	
	VL < 200 copies/mL	PREDZISTA[32]
S: IC_{50} FC < 10	68%	
I: IC_{50} FC 10–40	46%	
R: IC_{50} FC > 40	20%	
Baseline darunavir RAMs		
Number	VL < 50 copies/mL	POWER 1, 2, 3[31]
0	65%	
1	50%	
2	40%	
3	20%	
≥4	10%	
Number	VL < 200 copies/mL	PREDZISTA[32]
<4	89%	Identified darunavir RAMs differ from IAS, Stanford and
4–5	52%	ANRS mutations
>5	0%	
Activity of background antiretroviral drugs		
GSS	VL < 50 copies/mL	POWER 1, 2[19]
0	20%	GSS calculated as the sum of each drug's score:
1	50%	0 for resistant by genotype, 1 for susceptible
≥	56%	
GSS	VL < 200 copies/mL	PREDZISTA[32]
0 0.5	20%	GSS calculated as the sum of each drug's score: 0 for
1–1.5	59%	resistant by genotype, 0.5 for possibly resistant, 1 for
2–3	70%	susceptible
Inhibitory quotients		
vIQ	$\Delta VL > -1$ $\log_{10}$	POWER 1, 2[38]
≤0.1	32%	
0.1 to ≤0.4	61%	
0.4 to ≤1.4	80%	
>1.4	84%	
vIQ	VL < 50 copies/mL	Darunavir salvage therapy in PI-experienced adults[39]
≤1.5	29%	
>1.5	71%	
gIQ	VL < 200 copies/mL	PREDZISTA[32]
≤1.8	0%	
>1.8	55%	

Notes and Abbreviations: IC_{50}, 50% inhibitory concentration in vitro; FC, fold change in IC_{50} relative to wild-type IC_{50}; VL, viral load; RAMs, resistance associated mutations; GSS, genotypic sensitivity score, which quantifies the activity of the additional antiretroviral drugs in the regimen based on genotype; vIQ, virtual phenotypic inhibitory quotient, which is the ratio of the trough darunavir concentration to the IC_{50} of the dominant strains as measured by virtual phenotype; gIQ, genotypic inhibitory quotient which is the ratio of the trough darunavir concentration to the number of darunavir RAMs in the dominant viral strains.

In another, less PI-experienced cohort of 1021 patients who were failing PI therapy, and who had a median of 5 PI RAMS per patient, there was a lower prevalence of darunavir RAMs. I47V, I50V, 54L/M and L89V all had a frequency below 2.5%; L33F and I84V had rates of 11% and 14.5%, respectively.[21] Only 6.7% of the patients had ≥3 darunavir RAMs , and 68% had no darunavir RAMs. In those patients with ≥3 darunavir RAMs the mean number of RAMs to all PIs was 12.3 compared with 5.3 in the patients with <3 darunavir RAMs ($P < 0.0001$). Together with the

Table 8 Shared darunavir resistance mutations with other protease inhibitors[29]

DRV	V11I	V32I	L33F	I47V	I50V	I54LM	T74P	L76V	I84V	L89V
ATV 21%		m	m		M	m			M	
f-APV 55%		m		m	M	m		m	M	
IDV 29%		m				m		m	M	
LPV 35%		M	m	M	m	m			m	
NFV 10%									m	
SQV 18%						m			m	
TPV 29%			M	M		m	M		M	

Notes: Major darunavir mutations are in bold. Percentages are the number of shared mutations divided by the total number of resistance mutations for each drug.
Abbreviations: M, major mutation; m, minor mutation; ATV, atazanavir; f-APV, fosamprenavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; SQV, saquinavir; TPV, tipranavir.

POWER cohort, these data strongly reinforce that a large number of PI mutations accumulate prior to the emergence of darunavir RAMs.

In addition to an association with virologic efficacy of darunavir therapy, the baseline mutation profile has been shown to be an important predictor of the mutational pattern that emerges with treatment-associated failure of the drug. Genotypes were obtained at baseline and at the time of failure in a cohort of 25 treatment experienced patients, all of whom failed to achieve or maintain virologic suppression while receiving darunavir for at least 3 months.[33] Those with ≤1 baseline darunavir RAM selected ≤1 additional RAM at the time of failure, suggesting sub-optimal adherence was the likely cause. Those with ≥4 baseline RAMs also selected ≤1 additional RAM after failure, likely because the dominant viral isolate was already largely resistant to darunavir at baseline. In contrast, two-thirds of the patients with 2 to 3 baseline RAMs selected 2 to 5 additional RAMs after failure. Furthermore, among those with viral replication for >24 weeks on darunavir, additional RAMs were selected in 93%, vs only 40% of those who stopped darunavir earlier.

In the much larger POWER cohort, at 24 weeks, overall there were 146 (31%) of 458 patients who either rebounded or never achieved virologic suppression.[31] In these, the most common observed mutation was V32I in 35%. This mutation is one of the major mutations associated with failure in the Stanford resistance database, although IAS does not list it as a major mutation.

Prior failure with tipranavir does not seem to substantially increase the risk of acquiring darunavir RAMs, consistent with the preservation of tipranavir IC_{50} discussed in the previous section. In a small cohort of 47 patients, the Stanford-based mutation score for darunavir did not significantly increase (worsen) after failure with tipranavir, compared with the score prior to starting tipranavir.[34] The authors hypothesize that the preservation of darunavir activity after failure with tipranavir may be explained by an overlap in primary RAMs between darunavir and tipranavir of only four mutations: 33F, 47V, 54M and 84V. Conversely, viral isolates that are resistant to darunavir can be resistant in vitro to all other PIs except tipranavir.[12] In clinical studies, patients who fail darunavir are more likely to preserve the activity of tipranavir than any other PI.[33,35]

In summary, 11 darunavir RAMs have been identified which contribute to therapeutic failure, especially when ≥3 are present at baseline, and which emerge with failure of darunavir, especially if failing therapy is prolonged more than 6 months. A high number of PI RAMs must generally accumulate prior to selection of darunavir RAMs, suggesting a high genetic barrier that delays emergence of darunavir resistance. Failure with darunavir appears to preserve activity to tipranavir, if present at baseline. The converse is also true, that failure with tipranavir appears to preserve the activity of darunavir.

Phenotypic susceptibility and outcomes

According to the vircoTYPE HIV-1® virtual phenotypic database (Virco, Inc.), there is a 20% loss of clinical activity when the in vitro IC_{50} of the patient's dominant viral strain is increased by 10-fold relative to wild type, and an 80% loss of activity when the IC_{50} is increased by 106.9-fold.[36] For the Phenosense® assay (Monogram, Inc.), the lower cutoff is the same, but due to methodologic differences the higher cutoff that defines resistance is a 40-fold increase in the IC_{50},[37] considerably lower than the vircoTYPE cutoff; therefore, resistance results from these two tests are not fully interchangeable.

In combined analysis of all three POWER studies, baseline virtual phenotypic susceptibility was highly predictive of the percent of patients with a viral load <50 copies/mL at week 48. Relative to wild-type virus, a <10-fold change

in protein-adjusted IC_{50} was associated with a 50% rate of suppression, compared with 25% in the intermediate range (10- to 40-fold), and 13% in the resistant range (>40-fold).[31] In the PREDZISTA study of 65 PI-experienced patients receiving darunavir as a component of salvage therapy, baseline fold change was also associated with outcome, ranging from virologic response in 68% with a fold change <10, to only 20% with a fold change >40.[32] Baseline resistance to darunavir was extremely low in both the ARTEMIS[15] (treatment-naïve) and TITAN[24] (moderately treatment-experienced) studies, precluding any conclusions about relationship to the odds of virologic suppression.

Failure with darunavir appears to preserve the phenotypic sensitivity of tipranavir, the other nonpeptidic PI, if active at baseline. In the POWER cohort, those who failed darunavir therapy predictably had a 24-week median darunavir IC_{50} 91.1-fold higher than wild type IC_{50}, compared to a baseline fold change of only 12.6.[31] Despite this increase in darunavir IC_{50}, the median fold change in tipranavir IC_{50} was 2.6 at 24 weeks compared to 3.1 at baseline. Over 80% of isolates susceptible to tipranavir at baseline were still susceptible to tipranavir after failure with darunavir.

In summary, in large numbers of treatment-experienced patients, baseline phenotypic susceptibility was an important predictor of virologic suppression after starting darunavir-based combination antiretroviral therapy. Failure with darunavir does not appear to increase the tipranavir IC_{50}, suggesting that the drugs have different mutational pathways to resistance. This will be discussed more in the next section.

Concentrations, inhibitory quotients and outcomes

In the POWER 1 and 2 cohorts, there was a statistically significant, but weak relationship between darunavir plasma AUC ($P = 0.026$) or trough concentration ($P = 0.010$) and >1 $\log_{10}$ reduction in viral load at week 24 compared with baseline.[38] Baseline fold-change in darunavir IC_{50} and vIQ were each more strongly associated with the same outcome ($P < 0.001$ for both). Among those patients with a vIQ in the highest quartile (>1.4), 84% had a viral load drop of more than 1 $\log_{10}$ at week 24, compared to only 32% of patients with a pIQ in the lowest quartile (<0.1).

A smaller study in 37 PI-experienced adults also found an association between baseline vIQ and response, identified by viral suppression <50 copies/mL after 48 weeks of darunavir plus optimized background therapy.[39] By Receiver-Operator Curve (ROC) analysis, the vIQ which best discriminated responders from nonresponders was 1.5. Among responders, 70.8% had a vIQ ≥ 1.5, vs only 29.2% in nonresponders ($P = 0.028$). The median decrease in viral load from baseline in those with a vIQ > 1.5 was 2.5 $\log_{10}$ copies/mL, compared with only 0.27 $\log_{10}$ copies/mL for those with a vIQ < 1.5 ($P = 0.004$). In contrast to the POWER cohort, darunavir trough concentration (P = 0.377), baseline PI RAMs ($P = 0.918$), baseline darunavir RAMs ($P = 0.918$), and baseline fold-change in darunavir IC_{50} ($P = 0.651$) were not significantly different in responders vs nonresponders.

The above study also examined the relationship between gIQ and virologic outcome. By ROC analysis, the gIQ which best discriminated responders from nonresponders was 2.4, but the percent of responders higher than this threshold was not significantly different from the percent of nonresponders (71.4% vs 43.8%, $P = 0.105$). The median decrease in viral load from baseline in those with a gIQ > 2.4 was 2.5 $\log_{10}$ copies/mL, compared with 1.6 $\log_{10}$ copies/mL for those with a gIQ < 2.4 ($P = 0.139$). However, in the PREDZISTA study, a baseline gIQ of ≥ 1.8 was predictive of response (viral load <200 copies/mL) after 12 weeks of darunavir-based therapy, with 55% of those with gIQ < 1.8 failing to respond, vs none with gIQ ≥ 1.8 ($P < 0.001$).[32]

In summary, the antiviral efficacy of darunavir in patients is largely driven by susceptibility of the patient's dominant viral strain, whether measured by phenotype or genotype. However, incorporation of darunavir plasma concentrations in the form of an IQ contributes some additional information to prediction of virologic response. A possible vIQ target is 1.5, while a candidate gIQ is 1.8. These targets may be helpful in individual patients, but it is premature to recommend determination of the IQ as part of routine care.

Safety and tolerability

Major adverse effects in the DELPHI, POWER, ARTEMIS and TITAN trials are summarized in Table 5 and detailed here. In the DELPHI cohort, as might be expected in chronically ill children, average baseline height and weight were both 1.4 standard deviations below the mean of age-matched healthy children. At week 48, mean z-score had increased by 0.1 ($P = 0.136$) for height and 0.2 ($P = 0.003$) for weight, indicating that the children were growing and gaining weight faster than age-matched peers. There were only two clinical adverse effects greater than grade 1 and judged to be treatment related: diarrhea and rash. Neither were treatment limiting. Laboratory abnormalities greater than grade 1 included a decreased absolute neutrophil count

(13%), increased pancreatic amylase (11%), increased alanine aminotransferase (ALT, 6%) and aspartate aminotransferase (AST, 5%), and lipase (4%). Again, none resulted in cessation of darunavir. Darunavir significantly reduced fasting triglyceride levels to within the normal range for adults. In contrast, total cholesterol, LDL and HDL all increased significantly, but remained below normal adult values. Approximately half of the children were receiving lopinavir/ritonavir at the time of study entry.

In the POWER 1 and 2 studies,[19] the rates of adverse events higher than control were nausea (darunavir 18%/ control 13%), nasopharyngitis (14%/11%), upper respiratory infection (12%/7%) and herpes simplex (12%/2%). The most common treatment-emergent grade 3 and 4 laboratory abnormalities in the darunavir group higher than control were increased triglycerides (15%/7%), increased pancreatic amylase (6%/5%), increased total cholesterol (7%/2%), and increased pancreatic lipase (5%/1%). No cases of clinical pancreatitis were observed in patients with lipase abnormalities.

In ARTEMIS, darunavir was also associated with increases in triglycerides (3%), pancreatic amylase (7%), and total cholesterol (13%), but the lipid abnormalities were significantly higher in the lopinavir arm (11% and 23% for triglycerides and cholesterol) and similar for amylase (5%).[15] In TITAN, no adverse events >Grade 1 that were judged to be related to study drug were more common in the darunavir arm.[24] Laboratory abnormalities >Grade 1 and at least possibly related to study drug which were more common in the darunavir arm included total cholesterol (32%/29%), low-density lipoprotein (19%/17%), pancreatic amylase (11%/9%), and pancreatic lipase (5%/4%).

The package insert contains additional safety information from the combined analysis of more than 3000 patients exposed to darunavir, and these are summarized in Table 9.[12] Adverse reactions noted in all Phase II tests with >Grade 1 intensity include abdominal pain, acute hepatitis, acute pancreatitis, anorexia, asthenia, diabetes mellitus, diarrhea, fatigue, headache, hepatic enzyme increased, hypercholesterolemia, hyperglycemia, hypertriglyceridemia, immune reconstitution syndrome, low density lipoprotein increased, nausea, pancreatic enzyme increased, rash, Stevens-Johnson Syndrome and vomiting.

In prelicensure testing, 0.5% of patients developed hepatitis, and additional postlicensure reports of hepatitis have accrued. Most patients had underlying or concomitant processes, such as co-infection with hepatitis B or C, which predisposed them to hepatitis. Nonetheless, baseline and routine monitoring of AST/ALT is recommended, with increased frequency in those who are at risk prior to starting darunavir. Rashes were noted in 10%, and were typically mild to moderate, occurred during the first month of therapy, and resolved spontaneously without the need for treatment discontinuation. Severe rash, accompanying a systemic hypersensitivity reaction with fever and elevated hepatic transaminases, occurred in 0.4% of patients, and Stevens-Johnson was reported in 0.1%. Darunavir does contain a sulfa moiety, and thus should be used with caution in patients who have a sulfa allergy, although in clinical trials, the incidence of rash/hypersensitivity was the same regardless of the history of sulfa allergy. There have been reports of increased hemophilia A- or B -associated bleeding, in some cases requiring additional Factor VIII. Half of the cases did not result in discontinuation of the drug, and a causal relationship has not been established. Adverse effects common to all PIs, such as hyperglycemia, onset or worsening of diabetes mellitus, fat redistribution and immune reconstitution syndrome have all been reported for darunavir.

Finally, there is a specific warning in the package insert regarding use in young children.[12] Due to observed toxicity and mortality in juvenile rats dosed with darunavir from 20 mg/kg to 1000 mg/kg up to days 23 to 26 of age, use of darunavir in children under 6 years of age is currently not recommended, although as mentioned previously, application for licensure in patients as young as 3 years of age is currently underway in Europe.

In summary, darunavir has a safety profile in children older than 6 years of age that is comparable to that observed in more than 3000 adults, with the main adverse effects related to gastrointestinal symptoms, lipid abnormalities, pancreatic enzyme elevations, and probable immune reconstitution phenomena. Overall, rates of these adverse events are similar to or better than comparator regimens, and no "black box warnings" have been identified by the FDA.

Options for salvage therapy in children and adolescents

The most recent US Department of Health and Human Services guidelines for antiretroviral therapy in children and adolescents contain a newly updated section on recommended choices for the next antiretroviral regimen for treatment failure with evidence of drug resistance.[3] As for adults, the goal is <50 viral copies/mL plasma, recognizing that this is not always possible. The strategy to select the salvage regimen is methodical, but becomes increasingly difficult as resistance accumulates, particularly in children who have fewer licensed therapeutic options than adults.

Table 9 Rates of darunavir adverse events and laboratory abnormalities observed in treatment-experienced adults, Phase III clinical trial (adapted from US Package Insert)[12]

		Darunavir/ritonavir 600/100 mg twice daily + optimized background N = 298	Lopinavir/ritonavir 400/100 mg twice daily + optimized background N = 297
Gastrointestinal disorders			
Abdominal distension		2%	<1%
Abdominal pain		5%	2%
Diarrhea		12%	18%
Dyspepsia		2%	<1%
Flatulence		<1%	1%
Nausea		7%	6%
Vomiting		4%	3%
General disorders and administration site conditions			
Asthenia		3%	1%
Fatigue		1%	1%
Metabolism and nutrition disorders			
Anorexia		1%	2%
Diabetes mellitus		<1%	0%
Musculoskeletal and connective tissue disorders			
Myalgia		1%	<1%
Nervous system disorders			
Headache		2%	3%
Psychiatric disorders			
Abnormal dreams		<1%	0%
Skin and subcutaneous tissue disorders			
Pruritus		<1%	1%
Rash		6%	3%
Laboratory parameters			
Alanine aminotransferase			
Grade 2	>2.5 to ≤5.0 × ULN	6%	5%
Grade 3	>5.0 to ≤10.0 × ULN	2%	2%
Grade 4	>10.0 × ULN	1%	2%
Aspartate aminotransferase			
Grade 2	>2.5 to ≤5.0 × ULN	4%	6%
Grade 3	>5.0 to ≤10.0 × ULN	2%	2%
Grade 4	>10.0 × ULN	<1%	2%
Alkaline phosphatase			
Grade 2	>2.5 to ≤5.0 × ULN	<1%	0%
Grade 3	>5.0 to ≤10.0 × ULN	<1%	<1%
Grade 4	>10.0 × ULN	0%	0%
Hyperbilirubinemia			
Grade 2	>1.5 to ≤2.5 × ULN	0%	1%
Grade 3	>2.5 to ≤5.0 × ULN	<1%	0%
Grade 4	>5.0 × ULN	<1%	0%
Triglycerides			
Grade 2	5.65–8.48 mmol/L 500–750 mg/dL	11%	11%

(*Continued*)

Table 9 (*Continued*)

		Darunavir/ritonavir 600/100 mg twice daily + optimized background N = 298	Lopinavir/ritonavir 400/100 mg twice daily + optimized background N = 297
Grade 3	8.49–13.56 mmol/L 751–1200 mg/dL	7%	9%
Grade 4	>13.56 mmol/L >1200 mg/dL	2%	5%
Total cholesterol			
Grade 2	6.20–7.77 mmol/L 240–300 mg/dL	24%	19%
Grade 3	>7.77 mmol/L >300 mg/dL	8%	11%
Low-density lipoprotein cholesterol			
Grade 2	4.13–4.90 mmol/L 160–190 mg/dL	13%	11%
Grade 3	≥4.91 mmol/L ≥191 mg/dL	7%	8%
Elevated glucose levels			
Grade 2	6.95–13.88 mmol/L 126–250 mg/dL	8%	9%
Grade 3	13.89–27.75 mmol/L 251–500 mg/dL	<1%	<1%
Grade 4	>27.75 mmol/L >500 mg/dL	<1%	0%
Pancreatic lipase			
Grade 2	>1.5 to ≤3.0 × ULN	2%	4%
Grade 3	>3.0 to ≤5.0 × ULN	2%	<1%
Grade 4	>5.0 × ULN	<1%	0%
Pancreatic amylase			
Grade 2	>1.5 to ≤2.0 × ULN	6%	6%
Grade 3	>2.0 to ≤5.0 × ULN	6%	3%
Grade 4	>5.0 × ULN	0%	0%

Abbreviations: ULN, upper limit of normal.

Optimally, all regimens should contain at least two, but preferably three fully active drugs.

For children failing an NNRTI-based regimen, the next regimen should be based on a PI. This is because primary resistance to either efavirenz or nevirapine (the first generation NNRTIs) confers resistance to the other drug, via the K103N mutation. Currently, the second-generation NNRTI, etravirine, which is active against many isolates that are resistant to first-generation NNRTIs, is not approved under the age of 18. This is likely to change in the near future, as Phase 1 testing in children is complete[40] and a proposed dose of 5.2 mg/kg twice daily will be tested in the currently enrolling Phase 2 PIANO (Pediatric trial with Intelence as an Active NNRTI Option) study of treatment-experienced children and adolescents over the age of 6 years.[41]

Conversely, failure on a PI-based regimen leaves several options for subsequent therapy depending on prior exposure and tolerability concerns. These options are NNRTI-based therapy, alternative PI-based therapy with ritonavir boosting, or NNRTI + boosted PI-based therapy. Finally, in the setting of failure with prior exposure to both PIs and NNRTIs, the guidelines recommend either a newer ritonavir-boosted PI (darunavir or tipranavir), dual-boosted PI combinations (lopinavir/ritonavir plus either atazanavir or saquinavir), and/or the use of efuvirtide, etravirine, raltegravir, or maraviroc.

In these "deep salvage" scenarios, pediatric providers can encounter the need for drugs with no FDA-licensure in the pediatric population (Table 1), or even no published data. In general, newer therapeutic classes or newer drugs

in older classes will be required to treat these patients. Since maraviroc and raltegravir are not approved for use under the age of 16 years, and dosing information is unavailable for either drug in children, treatment with these agents is currently best initiated in the context of a clinical trial. Etravirine is not yet licensed for those less than 16 years of age, and although there is a candidate pediatric dose, safety and efficacy of this dose have not yet been established.

In the guidelines,[3] lopinavir/ritonavir is currently listed as a preferred agent for initial therapy in children, and therefore would be the preferred agent for salvage therapy after failure with NNRTIs or perhaps another PI such as nelfinavir. It has been shown to be safe, effective, and durable in children and adolescents in this setting.[42,43] Fos-amprenavir/ritonavir has been shown to be noninferior to lopinavir/ritonavir in the treatment of treatment-naïve adults,[44] and to have good long-term virologic suppression in a noncomparative study of treatment-experienced adults,[45] but it has not been studied for salvage therapy in children.

Tipranavir has been studied in treatment-experienced children and is the drug most likely to be considered against darunavir for deep salvage therapy due to the largely non-overlapping resistance profiles (see section on Resistance Mutations above). Table 10 summarizes the comparison between darunavir and tipranavir, which is detailed here. The Pediatric AIDS Clinical Trials Group (PACTG), now the International Maternal Pediatric Adolescent AIDS Clinical Trials (IMPAACT) group co-sponsored the P1051 study with the manufacturer to evaluate the safety, tolerability and efficacy of tipranavir in treatment-naïve and -experienced children aged 2 to 18 years, although 97% of the enrollees were treatment-experienced.[46] Baseline characteristics of the P1051 study population (n = 115) were similar to the DELPHI participants, with a median of 7 antiretroviral drugs used previously and 13 PI mutations per patient. There were two doses studied, the higher of which was tipranavir 375 mg/m^2 plus ritonavir 150 mg/m^2 twice daily (n = 57), and was the dose that was eventually licensed by the FDA. In that group, 35.1% had a viral load of <50 copies/mL at 48 weeks and a median change in CD4+ cell count of +59 cells/mm^3. A high percentage of children in the high-dose cohort experienced adverse effects, the most common being vomiting (42%), cough (30%), diarrhea (26%), pyrexia (21%), nausea (18%), nasopharyngitis (12%) and headache (11%). Overall, 60% of the high-dose participants had an adverse effect judged to be related to the study drug in some way, and 7% stopped the drug due to the adverse effect. Grade 3 elevations in ALT occurred in 6%; bleeding occurred in 14% of those receiving capsules; there were no reported Grade 3 or higher elevations in triglycerides.

The overall proportion of patients with a serious adverse event was 25%, and this was marginally significantly higher

Table 10 Comparison between darunavir and tipranavir

	Darunavir	Tipranavir
FDA licensure		
Age	≥6 years of age	≥2 years of age
Pediatric Indication	Treatment-experienced	Treatment-experienced
Available formulations	75, 300, 400 and 600 mg film-coated tablets	250 mg capsules 100 mg/mL solution
Dosing frequency	Twice daily	Twice daily
Daily pill burden (maximum dose)	4	8
Drug interactions	+++ (largely due to ritonavir)	++++ (due to tipranavir and ritonavir)
	DELPHI, n = 80[10]	P1051, n = 115[46]
Baseline		
Prior ARV exposure (median number)	9	7
PI resistance mutation (median number)	11	13
48-week efficacy		
VL < 50 copies/mL	48%	35%
ΔCD4+ cells/mm^3	+147	+59
Rate of adverse effects		
Any	94%	94%
Serious	14%	25%

Abbreviations: ARV, antiretroviral; PI, protease inhibitors; VL, viral load.

than in the DELPHI study,[10] where the rate was 14% ($P = 0.05$, Chi square). The proportions of patients in the DELPHI and P1051 studies with any adverse event were the same: 94% vs 94%.

In summary, then, how does tipranavir compare with darunavir? Both are dosed with ritonavir, and both are administered twice daily. Tipranavir has tablet and liquid formulations, while darunavir is only supplied as tablets. Although the dosing frequency of each is the same, the pill burden for the full adolescent dose is lower for darunavir/ritonavir, with 2 tablets twice daily, vs 4 tablets twice daily for tipranavir/ritonavir. Darunavir is licensed for children as young as 6 years of age, while tipranavir is licensed for those as young as 2 years of age. Efficacy rates are similar, or slightly higher for darunavir. The rate of serious adverse effects in the DELPHI study for darunavir was less than in the P1051 study for tipranavir, but the overall rate of adverse events, without regard to cause, was the same for the two drugs. Drug interaction potential for both drugs is high, but somewhat higher for tipranavir due to its ability to broadly induce and inhibit the activity of numerous drug metabolizing enzymes.[47] In our clinic, which provides care to over 100 HIV-infected children and adolescents, we prefer to use darunavir before tipranavir due to darunavir's lower overall pill burden, lower ritonavir dose, and more predictable drug interactions; however, available evidence does not distinguish a preferred order of sequencing darunavir and tipranavir based on efficacy.

Conclusions/recommendations

Darunavir offers a safe and potent new choice of therapy to clinicians who care for HIV-infected children and adolescents. Because it has not been studied in treatment-naïve children, and there are numerous other first-line agents, and because laboratory evidence indicates that isolates which become resistant to darunavir can be resistant to all other PIs except tipranavir, use of darunavir should be restricted to salvage therapy. In this role it has activity against isolates which are highly resistant to other PIs. There are consistent genotypic and phenotypic predictors of virologic response to darunavir therapy to aid clinicians in evaluating the likelihood of success prior to initiating therapy. Additionally, there are less extensive data supporting phenotypic or genotypic inhibitory quotients which could be used to adjust therapy in selected patients if necessary.

Currently, the most likely pediatric population for whom darunavir would be useful is those who were infected with HIV at or near the time of birth and who have developed substantial antiretroviral drug resistance as they have matured. Transmission of multi-drug resistant HIV from mother to child is thus far very rare, and limited to case reports.[17,48,49] Adolescents who are infected through sexual contact or intravenous drug abuse generally will mature into adulthood before they have sufficient antiretroviral exposure to accumulate large numbers of resistance mutations which would warrant darunavir therapy.

Therapy for perinatally infected adolescents with multi-drug resistant virus remains extremely challenging due to adherence and other psychosocial issues.[3,50] Nonetheless, for selected children and adolescents who have likely already failed NNRTI-based therapy, and regimens based on atazanavir and lopinavir, darunavir with ritonavir offers a well tolerated, potent combination, with a relatively low pill burden, and which can have a substantial chance of virologic and immunologic benefit even with few additional active agents.

Disclosure

The authors declare no conflicts of interest.

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