PEDIATRIC ANTIRETROVIRAL DRUG INFORMATION

OVERVIEW: PEDIATRIC ANTIRETROVIRAL DRUGS

Members of the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children have developed this Pediatric Antiretroviral Drug Information Supplement. As new information becomes available, the supplement is updated. This document contains detailed information about the different classes of antiretroviral agents (ARVs), and should be used in conjunction with the Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (http://AIDSinfo.nih.gov/). Dosing information can be found in Appendix A of those Guidelines. Additionally, antiretroviral drug information updates, labeling changes, and safety warnings may be accessed by subscribing to the U.S. Food and Drug Administration (FDA) HIV/AIDS e-mail list at: http://www.fda.gov/oashi/aids/email.html.

Over the last two decades, therapeutic strategies for the treatment of pediatric patients with HIV infection have expanded dramatically from treatment with a single medication to combination therapy that includes up to five different classes of antiretroviral agents. As of February 2008, a total of 25 antiretroviral drugs have been approved for use in HIV-infected adults and adolescents: 14 of these have an approved pediatric treatment indication (noted with * below), and 13 are available as a pediatric formulation or capsule size. These agents are the CCR5 antagonist (maraviroc) and fusion inhibitor (enfuvirtide*), which prevent viral entry; the nucleoside/nucleotide reverse transcriptase inhibitors (abacavir*, didanosine*, emtricitabine*, lamivudine*, stavudine*, tenofovir, zalcitabine, and zidovudine*) and non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz*, etravirine, and nevirapine*), which act at the early stage of replication, prior to viral integration into the host genome; one inhibitor of viral genome integration into host genetic material (raltegravir); and the protease inhibitors (amprenavir, atazanavir, darunavir, fosamprenavir*, indinavir, lopinavir/ritonavir*, nelfinavir*, ritonavir*, saquinavir, and tipranavir), which exert their effects when the integrated HIV genome is subsequently expressed, by interfering with cleavage of HIV proteins by the viral protease. New classes of antiretroviral agents, such as maturation inhibitors, are currently under investigation.

Of the 25 ARVs that have been approved, 3 are no longer being manufactured either because of the development of improved formulations (i.e., amprenavir* replaced by fosamprenavir) or because of limited use (i.e., delavirdine and zalcitabine).

Entry and Fusion Inhibitors

Two antiretroviral drugs that interfere with sequential steps involved in the penetration of target cells by HIV are now available as therapeutic options for treatment experienced patients. HIV enters target cells via a multistep process which begins when HIV binds to the CD4 receptor, leading to conformational changes in the viral gp120 envelope protein. Next, gp120 binds to chemokine receptor molecules, which function as coreceptors for HIV. Chemokine receptor engagement triggers conformational changes in the HIV gp41 envelope protein, leading to fusion of the membranes surrounding HIV and the target cell, resulting in delivery of the viral core into the cytoplasm.

Maraviroc is an oral agent that has been recently licensed for use in treatment-experienced HIV-infected adults. It binds to and alters the structure of the CCR5 chemokine receptor, preventing it from being used as a coreceptor by HIV. Since some strains of HIV can also infect cells by using the CXCR4 chemokine receptor molecule as a coreceptor, maraviroc is ineffective in individuals who currently harbor CXCR4 tropic or dual-tropic (CCR5 and CXCR4-using) virus. Consequently, determining the tropism of virus infecting an individual should be determined before instituting therapy with a maraviroc containing regimen. Maraviroc is a cytochrome P450 (CYP) 3A and p-glycoprotein (Pgp) substrate, and extensive pharmacokinetic studies in adults have shown that dosage adjustments are needed when it is administered in concert with CYP- or Pgp-modulating medications. Experience with maraviroc is limited, but its safety profile appears similar to most other antiretroviral agents. Hepatotoxicity has been reported with use of maraviroc; evidence of a systemic allergic reaction (e.g., pruritic rash, cosinophilia, or elevated IgE) may occur prior to the development of hepatotoxicity [1].
Enfuvirtide (T-20) is the first drug of the fusion inhibitor class of antiretroviral drugs to be approved; this drug interacts with components of the HIV envelope to prevent fusion of the virus with the host cell membrane. Enfuvirtide requires twice daily subcutaneous injections. The high incidence of local injection site reactions (98%) limits the use of the fusion inhibitors in pediatric patients.

### Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors

The nucleoside analogue reverse transcriptase inhibitors (NRTIs) were the first class of antiretroviral drugs available for the treatment of HIV infection. The NRTIs are potent inhibitors of the HIV reverse transcriptase enzyme, which is responsible for the reverse transcription of viral RNA into DNA; this process occurs prior to integration of viral DNA into the chromosomes of the host cell. The antiviral activity of NRTIs depends upon intracellular serial phosphorylation by host cellular kinases to the active triphosphate drug. The phosphorylated drug competitively inhibits viral reverse transcriptase and, following incorporation of the drug into the growing DNA chain, terminates further elongation of viral DNA. Because these drugs act at a pre-integration step in the viral life cycle, they have little to no effect on chronically infected cells, in which proviral DNA has already been integrated into cellular chromosomes. Like the NRTIs, nucleotide reverse transcriptase inhibitors (NtRTIs) also competitively inhibit the viral reverse transcriptase, but because the nucleotide drugs already possess a phosphate molecule (the NRTIs do not), the nucleotide drugs bypass the rate-limiting initial phosphorylation step required for activation of NRTIs.

Although resistance to these agents eventually develops during the course of long-term single drug therapy, combination therapy with these drugs may prevent, delay, or reverse the development of resistance. One notable exception is lamivudine (3TC) and emtricitabine (FTC), with which a single point mutation can confer resistance in as little as 4 to 8 weeks when given as monotherapy or in combination with an antiretroviral regimen that does not fully suppress viral replication (e.g., dual NRTI therapy with zidovudine [ZDV]/3TC).

Evidence suggests that polymerase gamma, the DNA polymerase present in mitochondria, is inhibited by NRTIs/NtRTIs. It is thought that this leads to depletion of mitochondrial DNA (mtDNA) through inhibition of mtDNA synthesis. This depletion may contribute to many of the toxicities associated with NRTIs/NtRTIs. Unusual, but significant, serious toxicities that can occur in patients exposed to these agents include lactic acidosis, hepatic steatosis, pancreatitis, myopathy, cardiomyopathy, peripheral neuropathy, and rapidly ascending muscular weakness. Interestingly, although some toxicities (e.g., lactic acidosis) may occur with all NRTI drugs, other toxicities (such as peripheral neuropathy) may predominantly occur with specific NRTIs, suggesting diverse mitochondrial effects of the drugs that may be dependent on varying ability to penetrate particular cell types. The relative potency of the NRTIs/NtRTIs in inhibiting polymerase gamma in vitro is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), and ZDV, with the lowest potency for 3TC, abacavir (ABC), and tenofovir disoproxil fumarate (TDF).

Evidence suggests that polymerase gamma, the DNA polymerase present in mitochondria, is inhibited by NRTIs/NtRTIs. It is thought that this leads to depletion of mitochondrial DNA (mtDNA) through inhibition of mtDNA synthesis. This depletion may contribute to many of the toxicities associated with NRTIs/NtRTIs. Unusual, but significant, serious toxicities that can occur in patients exposed to these agents include lactic acidosis, hepatic steatosis, pancreatitis, myopathy, cardiomyopathy, peripheral neuropathy, and rapidly ascending muscular weakness. Interestingly, although some toxicities (e.g., lactic acidosis) may occur with all NRTI drugs, other toxicities (such as peripheral neuropathy) may predominantly occur with specific NRTIs, suggesting diverse mitochondrial effects of the drugs that may be dependent on varying ability to penetrate particular cell types. The relative potency of the NRTIs/NtRTIs in inhibiting polymerase gamma in vitro is highest for zalcitabine (ddC), followed by didanosine (ddI), stavudine (d4T), and ZDV, with the lowest potency for 3TC, abacavir (ABC), and tenofovir disoproxil fumarate (TDF). The prevalence of mitochondrial-associated adverse effects in children is unknown.

A potentially fatal hypersensitivity reaction occurs in approximately 5% of adults and children receiving ABC. Before using ABC, patients must be cautioned about the risk of a serious hypersensitivity reaction and how to recognize symptoms. A genetic predisposition to this syndrome has been identified (HLA-B*5701) and patients with this HLA type should not be treated with ABC.

### Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

The non-nucleoside reverse transcriptase inhibitors (NNRTIs) have substantial and specific activity against HIV-1, but not HIV-2 or other retroviruses. Unlike the NRTIs, which require intracellular phosphorylation to become active and then cause premature termination of viral DNA synthesis, NNRTIs inhibit HIV DNA polymerase activities by noncompetitively binding to and disrupting a unique catalytic site of the reverse transcriptase enzyme. There are currently four NNRTIs approved for the treatment of HIV infection: nevirapine (NVP), delavirdine (DLV) (which is no longer commercially available), efavirenz (EFV), and etravirine (ETR).
All members of this class are metabolized by cytochrome P450 (CYP) enzymes, particularly CYP34A, and depending on the agent, may induce or inhibit the metabolism of other medications.

NNRTIs rapidly reduce viral load. However, drug resistance develops rapidly after initiation of NNRTI monotherapy or with use in a non-suppressive combination regimen, and cross-resistance readily occurs between EFV and NVP [9]. Sustained suppression of viral load has been achieved in patients who have been treated with regimens combining NNRTIs plus NRTIs or NNRTIs plus protease inhibitors (PIs). A 2-dose intrapartum/newborn NVP regimen has been shown to reduce the risk of perinatal HIV transmission by nearly 50% compared to an ultrashort intrapartum/1 week infant ZDV regimen [10].

NNRTIs are associated with several types of hepatic toxicity, including asymptomatic elevation in transaminases, clinical hepatitis, and hypersensitivity reaction with hepatitis [11]. In HIV-infected adults, risk factors for NVP hepatic toxicity include elevated baseline serum transaminases, hepatitis B or C infection, female gender, and higher CD4 cell counts (particularly women with CD4 cell counts >250 cells/mm³) [12]. However, in contrast to what has been reported in adults, serious liver dysfunction appears much less common in pediatric patients receiving NVP therapy [13].

Hypersensitivity reactions are reported more commonly with the NNRTIs than with other antiretroviral agents. EFV can cause adverse CNS effects, including confusion, hallucinations, and nightmares. EFV has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk). Use of EFV in the first trimester of pregnancy should be avoided, and before initiating EFV therapy, adult and adolescent women of childbearing potential should undergo pregnancy testing as well as counseling about the risk to a fetus and the need to avoid pregnancy.

ETR recently received FDA approval for use in combination with other antiretroviral agents in treatment-naive adult patients. ETR is an inducer of CYP3A4 and an inhibitor of CYP2C9 and CYP2C19 and there are many potential drug interactions, including with other ARVs. ETR should not be coadministered with other NNRTIs; unboosted PIs; RTV alone; or with the following boosted PIs: tipranavir (TPV)/RTV, fosamprenavir (F-APV)/RTV, or atazanavir (ATV)/RTV. The presence of the K103N resistance mutation associated with NVP and EFV resistance, did not affect the response rate to ETR in clinical trials. The presence at baseline of ≥3 IAS-USA-defined NNRTI substitutions results in decreased virologic response [14].

Integrase Inhibitors

A key event in replication of HIV and other retroviruses is the insertion of a DNA copy of the viral genome into the host cell chromosome, a process known as integration. A viral protein, integrase, is essential to this process. Integrase modifies the ends of newly reverse transcribed DNA, introduces breaks into chromosomal DNA, and transfers and joins the ends of the viral DNA to chromosomal DNA. Raltegravir, the first integrase inhibitor to receive approval for clinical use, is an oral agent that interferes with the strand transfer activity of integrase, blocking integration. When used in concert with other antiretroviral agents, including the fusion inhibitor enfuvirtide, marked suppression of HIV replication has been seen in studies involving treatment-experienced adults infected with virus with extensive drug resistance involving reverse transcriptase and protease inhibitors [15, 16]. Early results involving treatment naïve adults have also been promising, with most patients achieving suppression of HIV plasma viremia [16]. The pharmacokinetics, safety, and efficacy of raltegravir are currently unknown in children and adolescents <16 years of age, but pediatric studies have begun.

Protease Inhibitors

Protease inhibitors (PIs) inhibit the HIV protease enzyme, which is required to cleave viral polyprotein precursors and generate functional viral proteins. The protease enzyme is crucial for the assembly stage of the viral life cycle, which occurs after transcription of proviral DNA to viral RNA and translation of the RNA into viral proteins. Because PIs act at a post-
integration step of the viral life cycle, they are effective in inhibiting replication in both newly infected and chronically infected cells [17]. The PIs are potent antiretroviral agents, especially when used in combination with NRTI and/or NNRTI therapy [17]. Unlike the NRTI drugs, intracellular conversion of the parent compound is not required for activity of any of the PIs.

Resistance has been reported with all PIs when used as monotherapy, and can develop rapidly even with combination therapy if there is persistent viremia due to subtherapeutic drug concentrations (as can occur when there is inadequate dosing, poor drug absorption, rapid drug clearance, or inadequate adherence to the prescribed drug regimen). The patterns of resistance mutations are more complex than observed with the NRTIs and NNRTIs. A larger number of genotypic mutation sites are observed, and there is greater variability in the temporal pattern of development of these mutations and in the combination of mutations that lead to drug resistance. The mutation patterns associated with PI resistance overlap; resistance to one drug may result in reduced susceptibility to some or all of the other currently available PIs.

“Boosted” therapeutic regimens consisting of two PIs (e.g., ritonavir [RTV] plus saquinavir [SQV], amprenavir [APV], fosamprenavir [f-APV], atazanavir [ATV], or indinavir [IDV]) combined with one or two NRTIs are frequently used in adults with good results, especially in PI-experienced patients. However, with the exception of the coformulated PI lopinavir/ritonavir (LPV/RTV, Kaletra), there are currently limited data on safety and dosing of combination PI regimens in children. Thus, appropriate dosing of RTV-boosted PIs outside of LPV/RTV is less certain in children than adults, and requires administration of two separate drug formulations.

New onset diabetes mellitus, exacerbation of preexisting diabetes mellitus, and hyperglycemia have been reported in HIV-infected patients treated with any of the currently available PIs [18-21]. In some cases, diabetic ketoacidosis has occurred. The PIs have been associated with fat redistribution, lipodystrophy syndrome, and hyperlipidemia in both adults and children [22]. A potentially increased risk of cardiovascular disease and of bone disorders, such as osteoporosis and avascular necrosis, are currently being investigated.

PIs are metabolized in the liver via the CYP450 enzyme system. Clinically significant drug interactions may occur when a PI is administered concomitantly with other agents metabolized by the CYP450 system, especially those metabolized by CYP3A, CYP2D6, CYP2C9, and CYP2C19, and to a lesser extent by CYP2A6, CYP1A2, and CYP2E1. Increased or decreased plasma concentrations of either drug may occur and consequent clinical abnormalities may be seen. See the Pediatric Guidelines Appendix A: Characteristics of Available Antiretroviral Drugs Matrices 2–4 for a list of contraindicated medications. A complete list of potential drug interactions is provided by the PI manufacturer in the prescribing information, which should be consulted prior to initiating PI therapy or starting any new concomitant therapy in patients receiving PI-based regimens.

References:


Abacavir (ABC, Ziagen®)
URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
In December 1998, abacavir (ABC) was approved by the FDA for combination therapy in adults and children age 3 months or older, based on controlled trials in adults and children. The combination of ABC, lamivudine (3TC), and zidovudine (ZDV) in a single tablet formulation (Trizivir) for twice daily dosing in adults became available in November 2000. A new formulation combining ABC and 3TC (Epzicom) for administration as a single daily dose for adults was approved in August 2004.

ABC is a guanosine analogue nucleoside reverse transcriptase inhibitor (NRTI). ABC is anabolized intracellularly to carbovir triphosphate by enzymatic pathways distinct from other NRTIs [1]. Preliminary studies of carbovir triphosphate suggest persistence in lymphocytes, consistent with single daily ABC dose regimens approved for use in adults [2]. ABC crosses the blood-brain barrier, with a CSF-to-plasma concentration ratio of 36% [3]. Bioavailability is 83%, and mean systemic half-life is 1.5 hours. In humans, cytochrome P450 enzymes do not significantly metabolize ABC, and it in turn does not inhibit human CYP3A4, CYP2D6, or CYP2C activity at clinically relevant concentrations. The primary routes of elimination are metabolism by alcohol dehydrogenase and glucuronyl transferase.

Resistance
ABC resistance mutations have been seen at reverse transcriptase (RT) gene codons K65R, L74V, Y115F, and M184V both in vitro and in patients taking ABC [4, 5]. At least 2–3 mutations are required to reduce susceptibility by 10-fold. Mutations at codons M184V and L74V were most frequently observed in clinical isolates. ABC-resistant virus will be resistant to 3TC. While virus resistant to ZDV or 3TC alone may remain susceptible to ABC, virus resistant to both ZDV and 3TC is more likely to be cross-resistant to ABC. The combination of M184V with ZDV mutations gives rise to high-level ABC resistance [4]. While ABC may be included as a component of a treatment regimen for children who have failed prior antiretroviral therapy, it should be recognized that it is less likely to be active in children with extensive prior treatment with NRTIs. High rates of clinical failure and an accelerated selection of M184V and K65R have been reported when ABC is given in combination with 3TC and tenofovir disoproxil fumarate (TDF) as part of a triple NRTI-only regimen [6, 7].

Adverse Effects
Nausea and vomiting alone may occur in as many as one-third of children receiving ABC in combination with other antiretroviral agents. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ABC.

A potentially fatal hypersensitivity reaction occurs in approximately 5% of adults and children receiving ABC (see Matrix 1 in Appendix A). Symptoms include flu-like symptoms, respiratory symptoms, fever, rash, fatigue, malaise, nausea, vomiting, diarrhea, and abdominal pain. Patients developing these symptoms should have ABC stopped and not restarted, as hypotension and death have occurred with rechallenge. In a randomized study comparing ABC/ZDV/3TC to ZDV/3TC alone, 4 of 146 children receiving ABC and 2 of 44 children receiving ZDV/3TC and who switched to open label ABC therapy developed a hypersensitivity reaction, which resolved upon discontinuation of therapy [8]. Onset of the hypersensitivity reaction occurred between 1 to 2 weeks after ABC was started.

Some studies have suggested that development of the ABC hypersensitivity reaction may be associated with certain HLA genotypes (e.g., HLA-B*5701 genotype) [9, 10]. In a study in HIV-infected adults, pre-treatment screening for HLA-B*5701 prior to initiation of ABC treatment, with initiation of therapy only in adults who were negative for this HLA genotype, resulted in a significant reduction in the rate of ABC hypersensitivity reaction [11]. Genetic screening for HLA-B*5701
has been recommended in HIV-infected adults prior to initiation of ABC-based therapy. However, the utility and cost-effectiveness of genetic screening for a given population depends upon the prevalence of HLA-B*5701 in that population. In Caucasian populations in the United States, the prevalence of HLA-B*5701 is about 8%; however, in the United States, the prevalence is about 2.5% in African Americans; 2% in Hispanics; and 1% in Asians; and in sub-Saharan Africa, the prevalence is <1% [12]. In the United States, the majority of HIV-infected children are of minority race/ethnicity. Genetic screening for HLA-B*5701 should be considered for HIV-infected children prior to initiating ABC-based therapy. If HLA-B*5701 testing is performed, ABC should not be given to patients who test positive for HLA-B*5701.

When ABC is used, parents and patients must be cautioned about the risk of a serious hypersensitivity reaction (including patients who are HLA-B*5701 negative, as the risk is not completely eliminated); a medication guide and warning card should be provided to parents. Patients should also be advised to consult their physician immediately if signs or symptoms consistent with a hypersensitivity reaction occur. Children experiencing a hypersensitivity reaction should be reported to the Abacavir Hypersensitivity Registry (1-800-270-0425).

Pediatric Experience

ABC has been studied in HIV-infected children both separately and in combination with other antiretroviral drugs [3, 8, 13-21]. In the PENTA-5 trial, 130 HIV-infected antiretroviral-naïve children were randomly assigned to one of three different nucleoside analogue regimens: ZDV/3TC, ABC/ZDV, and ABC/3TC, with and without nelfinavir (NFV) [14]. The two ABC-containing regimens were associated with greater mean viral load decreases after 48 weeks of therapy than the ZDV/3TC regimen (-1.71, -2.17, and -2.63 copies/mL with ZDV/3TC, ABC/ZDV, and ABC/3TC, respectively). In this study, 4 children (3%) stopped ABC due to a possible hypersensitivity reaction. After 5 years of follow-up in the PENTA-5 study, children who were treated with ABC/3TC were significantly more likely to have HIV RNA levels <50 copies/mL than children treated with ZDV/3TC or ABC/ZDV (63% vs 25 % or 32%, p = 0.003), and had significantly better improvement in height for age and weight for age [21].

Pharmacokinetic studies of ABC in children <12 years of age have demonstrated that pediatric doses approximately twice the directly scaled adult dose may be necessary to achieve similar systemic exposure [15]. Dose regimens for adolescents have not been well studied during chronic therapy. Additional studies on the pharmacokinetics of ABC in adolescents 13–24 years of age are ongoing (PACTG 1052). The PENTA-13 trial studied once daily versus twice daily dosing of ABC in combination with 3TC in 24 children aged 2–13 years, showing equivalent AUC0-24 for both drugs and improved acceptability in the once daily dosing arm [17]. However, trough concentrations were lower for both ABC and 3TC in younger children (ages 2–6 years) receiving the once daily regimen [17]. More pharmacokinetic studies are needed to confirm that once daily dosing of ABC and 3TC can be safely used in children.

ABC has been studied as part of a PI-sparing three-drug NRTI regimen (ZDV, 3TC, and ABC) in antiretroviral-experienced children. In a study of 205 treatment-experienced children ranging in age from 0.7–13 years, only 10% of 102 children receiving ABC/ZDV/3TC had HIV RNA concentrations <400 copies/mL after 48 weeks of therapy. The combination of ABC/ZDV/3TC did result in a greater fall in viral load and increase in CD4 cell count than did ZDV/3TC [8]. In pediatric populations, triple NRTI-only combinations should be used only in special circumstances. A randomized trial in antiretroviral-naïve adults has shown that the combination of ZDV, 3TC, and ABC is virologically inferior when compared to the NNRTI efavirenz combined with 2–3 NRTIs [22]. Other trials involving triple NRTI regimens in antiretroviral-naïve adults have also shown decreased virologic potency, raising concern about the routine use of triple NRTI therapies, at least with the currently available drugs [7, 23, 24].

References:


Didanosine (ddI, Videx®)

URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
Didanosine (ddI) received FDA approval in 1991 for adults and for pediatric patients older than 6 months of age with advanced HIV infection who were intolerant to or deteriorating on zidovudine (ZDV). Since that time, the indications have been broadened and new formulations developed. In October 2000, a new delayed-release formulation of enteric-coated beadlets was approved for use in adults, allowing for once daily ddI administration in selected patients. In December 2004, a generic formulation of ddI delayed-release capsules for once daily administration was approved by the FDA.

ddI is a purine dideoxynucleoside analogue that requires intracellular phosphorylation in resting cells to become active. Despite lower cerebrospinal fluid (CSF) penetration than ZDV (CSF-to-plasma concentration ratio of 5%), early pediatric studies of ddI monotherapy demonstrated a 46% (range 12%–85%) improvement in neuropsychometric testing scores observed in some children; the improvement was correlated with ddI plasma concentration [1, 2]. ddI is unstable at acidic pH and is rapidly degraded unless given as the enteric formulation or combined with buffering agents or antacids. Bioavailability ranges from 20%–40% depending upon the formulation used. ddI’s plasma half-life is 0.5 to 1 hour, with renal elimination and metabolism by purine nucleoside phosphorylase. The intracellular half-life of ddI is 25 to 40 hours, and the long intracellular half-life allows for an extended dosing interval. Data from PACTG 144 suggest that systemic exposure (i.e., the AUC) to ddI in children remains similar in both the presence and absence of food [3]. This may allow for the relaxation of fasting state requirement in certain instances.

Resistance
Genotypic mutations at RT gene codons K65R, L74V, and M184V have been associated with ddI resistance. The most common mutation, L74V, is most frequently associated with diminished antiviral activity of ddI. Interestingly, isolates with this resistance mutation have increased susceptibility to ZDV [4]. Lamivudine (3TC)-resistant virus may have reduced susceptibility to ddI, but cross-resistance is not complete. High rates of clinical failure and an accelerated selection of M184V and K65R have been reported when ddI is given in combination with 3TC and tenofovir disoproxil fumarate (TDF) [5].

Adverse Effects
Fatal and nonfatal pancreatitis has occurred during therapy with ddI used alone or in combination regimens in both treatment-naïve and treatment experienced patients, regardless of degree of immunosuppression (see Matrix 1 in Appendix A). ddI should be suspended in patients with suspected pancreatitis and discontinued in patients with confirmed pancreatitis. Pancreatitis appears to be more common in adult patients and may be dose-related. It has occurred more commonly in patients with predisposing factors, including a prior history of pancreatitis, baseline elevation of serum transaminases, and concurrent administration of other drugs known to cause pancreatitis, such as pentamidine and d4T [6]. Hydroxyurea appears to increase the risk of pancreatitis when coadministered with ddI; this combination is not recommended.

ddI may cause peripheral sensory neuropathy. Asymptomatic peripheral retinal depigmentation has been observed in <5% of children receiving ddI, is not associated with loss of vision, and appears to reverse with discontinuation of therapy [7]. Diarrhea has been reported, and may be more related to the antacid/buffer with which the drug is formulated than to ddI itself. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside...
analogues alone or in combination, including ddI; the combination of d4T and ddI in pregnant women has been associated with fatal lactic acidosis and should only be used if no other alternatives are available.

Coadministration of TDF with ddI increases peak ddI concentrations and systemic exposure significantly and there is an increased risk of ddI-related toxicities when these drugs are administered together [8-10]. In addition, ddI in combination with lopinavir/ritonavir (LPV/RTV) and TDF may enhance the nephrotoxic potential of TDF [11, 12]. Perhaps because of increased exposure to ddI and resultant lymphocyte toxicity, the combination of ddI plus TDF has been associated with a decline in CD4 cell counts, even when plasma virus load remains low [13]. There are no data on coadministration of TDF and ddI in children except for a recent case report of a 12-year-old girl who developed nephrogenic diabetes insipidus, renal insufficiency, and Fanconi-like syndrome while taking TDF with both LPV/RTV and ddI [12].

**Pediatric Experience**

ddI has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs [2, 3, 14-30]. Recommended ddI doses in children have traditionally been between 90–150 mg per meter² body surface area per dose twice daily. Doses higher than 180 mg per meter² body surface area are associated with increased toxicity [2]. In a simulation based on ddI concentration data from 16 children, a dose of 90 mg per meter² body surface area was predicted to result in adequate drug exposure in only 57% of pediatric patients, compared to 88% of patients predicted at a dose of 120 mg per meter² body surface area [14]. This dose of 120 mg per meter² body surface area per dose twice daily has therefore become the “standard” dose of ddI for older infants and children. Data from multiple pediatric studies of ddI alone or in combination with other drugs, including a study of long-term ddI use (median duration of almost 2 years), show that ddI appears safe and is associated with clinical improvement, increase in CD4 count, and decrease in viral load [15-21].

Three major areas of controversy remain in the use of ddI in the treatment of children with HIV infection: 1) the appropriate dose to use in infants 2 weeks to 4 months of age, 2) the need to dose ddI on an empty stomach, and 3) the potential use of enteric-coated ddI (Videx EC) once daily in children.

The “usual pediatric dose” of 120 mg per meter² body surface area per dose twice daily was used successfully in combination therapy in infants 2–16 months of age, without significant toxicity [22]. Currently, the FDA recommends 100 mg per meter² body surface area per dose twice daily for infants from 2 weeks to 8 months of age, increasing to 120 mg per meter² body surface area per dose twice daily at age 8 months. However, two small studies suggest that higher AUCs are seen in infants <6 weeks of age, and that a dose of 100 mg per meter² body surface area per day (either as 50 mg per meter² body surface area per dose twice daily or 100 mg per meter² body surface area once daily) achieves AUCs consistent with those of higher doses in older children [23, 24]. Therefore, because of pharmacokinetic differences in younger infants (2 weeks to 4 months) compared to older children, a dose of 50 mg per m² of body surface area twice daily may be more appropriate in younger infants.

While the prescribing information recommends taking ddI on an empty stomach, this is impractical for infants who feed frequently, and may decrease medication compliance by increasing regimen complexity. A comparison of ddI given with or without food in children found that systemic exposure was similar, but with slower and more prolonged absorption [3]. To improve compliance, some practitioners recommend administration without regard to timing of meals for young children. However, there are inadequate data to allow a strong recommendation at this time, and it is preferred that ddI be administered under fasting conditions when possible.

Enteric-coated ddI (Videx EC) administered as a single dose of 240 mg per meter² body surface area has been shown to have similar plasma AUC (although lower peak plasma concentrations) compared to the equivalent dose of buffered ddI [24]. The resultant intracellular (active) drug concentrations are unknown. In 24 children with HIV infection, ddI at a dose of 180 mg per meter² body surface area once daily was compared to 90 mg per meter² body surface area twice daily, and the AUC was actually higher in the once daily group than in the twice daily group [25]. In fact, in 53 children with advanced symptomatic HIV infection, once versus twice daily ddI at a dose of 270 mg per meter² body surface area per day showed no difference in surrogate marker or clinical endpoints, except that weight gain was poorer in the children given once daily therapy [26].
trial of once daily HAART in 36 children aged 3–11 years that included ddI at a dose of 200–240 mg per meter² demonstrated safety and efficacy with 96 weeks of follow-up data [31]. Currently, enteric-coated ddI (Videx EC) is FDA approved only for persons over 18 years of age. However, enteric-coated ddI is the only tablet formulation available in the United States, so children treated with ddI tablets are administered that drug formulation, even though it is not FDA-approved.

In a study in the United States, long-term virologic suppression with a once daily regimen of efavirenz (EFV), emtricitabine (FTC) and ddI was reported in 37 treatment-naïve children, 3–21 years of age, participating in PACTG 1021 [32]. Eighty-five percent of subjects were able to achieve HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy.

References:


Emtricitabine (FTC, Emtriva™)
URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
Emtricitabine (FTC) was approved in July 2003 for treatment of HIV infection in adults aged ≥18 years and in September 2005 for treatment in children 3 months to 17 years of age. In August 2004, it was approved as a fixed-dose combination formulation of FTC and tenofovir disoproxil fumarate (TDF) (Truvada) for adults ≥18 years of age. In a study of antiretroviral-naïve adults, through week 48, FTC, TDF, and efavirenz (EFV) was superior to zidovudine (ZDV), lamivudine (3TC), and EFV in virologic suppression, CD4 response, and adverse events requiring discontinuation of study drugs [1]. Similar results were demonstrated through week 96 [2]. In July 2006, it was approved as a fixed-dose combination of FTC, TDF, and EFV (Atripla) for adults ≥18 years of age [3]. FTC is available as an oral solution of 10 mg/mL.

FTC is a synthetic cytosine nucleoside analogue (2’deoxycytidine). It differs only slightly in structure from 3TC (5-fluoro substitution), although its potency is on average five times higher in in vitro tests against HIV strains from primary clinical isolates [4, 5], and it may be more effective in vivo as well [6]. The IC_{50} of FTC ranged from 0.0013–0.64 µM when assessed in in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells against laboratory and clinical isolates of HIV. Like other NRTI drugs, FTC requires intracellular phosphorylation to become active. FTC is metabolized intracellularly and its primary route of elimination is via renal excretion without significant metabolic interactions with other antiretroviral drugs.

FTC is well absorbed rapidly following oral administration. Systemic exposure (AUC) is unaffected by administration of FTC with food. FTC pharmacokinetics are linear over a wide dosage range. The terminal half-life of FTC in plasma is 8 to 10 hours [7, 8].

Like 3TC, it is active against hepatitis B virus, but FTC has not been approved for use in patients with chronic hepatitis B or in patients coinfected with hepatitis B virus and HIV [9, 10]. “Flare-ups” of hepatitis B have been reported in HIV/hepatitis B coinfected patients after discontinuation of FTC therapy. Coinfected patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping FTC treatment [6].

Resistance
Like 3TC, resistance to FTC is associated with a single genotypic mutation at RT gene codon 184 [11]. Since in vitro data have shown that resistance to 3TC confers cross-resistance to FTC, FTC is not indicated after 3TC failure. FTC-resistant isolates are also cross-resistant to 3TC and ddC, but retain sensitivity to ABC, ddi, d4T, TDF, ZDV, and NNRTI drugs. Moreover, the M184V mutation enhances HIV susceptibility to ZDV, d4T, and TDF [12, 13]. HIV-1 isolates containing the K65R mutation, selected in vivo by ABC, ddi, TDF, and ddC, have reduced susceptibility to FTC [14]. An in vitro study of the drug resistance selection profile of FTC and TDF in combination showed that at drug concentrations set to closely mimic plasma drug concentrations in treated patients, an M184I mutation was observed first, followed directly by a double mutation, K65R and M184V [15].

Adverse Effects
FTC is well tolerated. The most common adverse events reported in clinical trials were headache, diarrhea, nausea, and rash, which were generally of mild to moderate severity and required drug discontinuation in only 1% of patients. Three patients were reported to have gastrointestinal intolerance to Truvada but were able to tolerate FTC or 3TC in combination with TDF [16]. Skin discoloration, manifested by hyperpigmentation of the palms and/or soles, has been observed, predominantly in non-Caucasian patients. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including FTC (see Matrix 1 in Appendix A).

Pediatric Experience
A single-dose pharmacokinetic study of FTC liquid solution and capsules was performed in 25 HIV-infected children 2–17 years of age [17]. FTC was found to be well-absorbed following oral administration, with a mean elimination half-life of 11 hours (range 9.7 to 11.6 hours). Plasma concentrations in children receiving the 6 mg/kg FTC once daily dose were approximately equivalent to those in adults receiving the standard 200 mg dose.
Based on this dose-finding study, FTC was given at a dose of 6 mg/kg once daily in combination with other antiretroviral drugs [18, 19]. In a pediatric phase II study, 51 antiretroviral-naïve children received FTC plus d4T and LPV/RTV while 31 treatment-experienced children were maintained on their initial regimens, but changed from 3TC to FTC [19]. Pharmacokinetic results were similar to the previous dose-finding study [17] although children <2 years of age may have more rapid absorption and more rapid clearance, resulting in lower trough levels [19]. Follow up data demonstrated that at week 48, 90% of the antiretroviral-naïve and 81% of the antiretroviral-experienced children achieved and/or maintained suppression of plasma HIV RNA ≤400 copies/mL [20]. There were 6 adverse events possibly or probably related to study drug and 8 grade 3 or 4 laboratory abnormalities.

FTC is under study in PACTG P1021 at a dose of 6 mg/kg (maximum 240 mg/day as liquid or 200 mg/day as capsules) in combination with ddI and EFV, all given once daily, in 37 antiretroviral-naïve HIV-infected children aged 3 months to 21 years [18]. This regimen has been well tolerated, and FTC and ddI concentrations have met the desired target study concentrations. Eighty-five percent of subjects were able to achieve HIV RNA <400 copies/mL and 72% maintained HIV RNA suppression to <50 copies/mL through 96 weeks of therapy. The median CD4 count rose by 329 cells/mm³ at week 96.

A study in South Africa evaluated the pharmacokinetics of FTC in 20 HIV-exposed infants under age 3 months, given as 3 mg/kg once daily for two 4-day courses, separated by an interval of ≥2 weeks [21]. FTC exposure (AUC) in neonates receiving 3 mg/kg FTC once daily was in the range of pediatric patients over age 3 months receiving the recommended dose of 6 mg/kg once daily and adults receiving the once daily recommended 200 mg FTC dose (AUC approximately 10 hr*ug/mL). FTC AUC decreased with increasing age over the first 3 months of life, correlating with an increase in total body clearance of the drug.

References:


3TC is active against hepatitis B virus, and “flare-ups” of hepatitis B have been reported in HIV/hepatitis B coinfected patients after discontinuation of 3TC therapy. Coinfected patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping 3TC treatment.

**Resistance**

When 3TC is administered as monotherapy, resistance emerges rapidly and is associated with a single genotypic mutation at RT gene codon 184. Resistance also develops rapidly (within weeks) when 3TC is used in non-suppressive combination antiretroviral regimens, such as dual NRTI therapy with ZDV/3TC [3]. Therefore, optimal use of 3TC is in a combination of ≥3 antiretroviral medications capable of providing full suppression of viral replication. 3TC-resistant virus may be partially cross-resistant to ddI and ddC. In vitro, development of the codon 184 mutation is associated with increased fidelity of the viral reverse transcriptase enzyme for its substrate [4]. It is speculated that this could influence the evolution of the virus and may prevent or delay the generation of drug resistant variants. For example, the 184 mutation is reported to suppress ZDV resistance in vitro. The 184 mutation suppresses the effect of some ZDV, d4T, and TDF resistance mutations, and the emergence of M184V may slow the development of resistance to these agents [5, 6]. Additionally, the M184I/V mutation is associated with diminished viral replicative fitness [7].

**Adverse Effects**

3TC is very well tolerated. The major reported toxicities are pancreatitis and peripheral neuropathy [1]. However, most reports of pancreatitis and neuropathy are from older studies in which children with advanced HIV were treated with other additional medications; many experts believe that the coadministered medications were more likely causative of toxicity than was 3TC. Headache, fatigue, and gastrointestinal upset have been described upon initiation of 3TC therapy but appear to lessen with use over time. Rarely, concurrent use of 3TC and ZDV has been associated with brisk, severe anemia [8]. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including 3TC (see Matrix 1 in Appendix A).

**Pediatric Experience**

3TC has been studied in HIV-infected children alone and in combination with other antiretroviral drugs, and extensive data demonstrate that 3TC appears safe and is associated with clinical improvement and virologic response [1, 9-23]. 3TC is commonly used in HIV-infected children as a component of a dual NRTI backbone, most often with ZDV or d4T, as part of HAART [13-17, 19-21, 23]. In one study, the NRTI background components of 3TC/ABC were superior to ZDV/3TC or ZDV/ABC in long-term virologic efficacy [24]. Because of its safety profile and availability in a liquid formulation, 3TC has been given to infants during the first 6 weeks of life [21].

3TC has become an important component of fixed-dose combination tablets with d4T and nevirapine that are available in some areas outside the United States [25, 26]. These fixed-dose combination tablets facilitate scaling-up of combination antiretroviral therapy in resource-poor areas because of their low pill burden, affordability, and potency, but can also limit treatment options for patients with virologic treatment failure [26].

Few data are available regarding once daily administration of 3TC in children. The pharmacokinetics of once daily vs. twice daily dosing of 3TC (8 mg/kg once daily vs. 4 mg/kg twice daily) and ABC (16 mg/kg once daily vs. 8 mg/kg twice daily) were evaluated in 20 HIV-infected children aged 2–13 years in the PENTA-13 trial; the plasma AUC0-24 for both drugs was similar with once and twice daily administration, but trough concentrations were lower for both ABC and 3TC in younger children (ages 2–6 years) receiving the once daily regimen, as were peak (Cmax) concentrations for 3TC [12]. No major toxicities were noted, and there was improved acceptability of the once daily dosing regimen [12]. At this time, once daily dosing of 3TC is only recommended for adolescents ≥16 years and ≥50 kg. More pharmacokinetic studies are needed to confirm that once daily dosing of ABC and 3TC can be safely used in children.

The dose of 3TC should be decreased in patients with renal insufficiency. 3TC should not be used concurrently with FTC because of the similar resistance profiles and lack of potential additive
benefits. It is possible that pharmacogenetic data will guide 3TC dosing in the future; a pilot study has shown that certain multi-drug resistance-associated protein genotypes are predictive of higher intracellular 3TC triphosphate concentrations [27].

References:


**Adverse Effects**

d4T is associated with a higher rate of adverse events than ZDV in adults and children receiving combination therapy [8-10]. One of the most significant toxicities associated with d4T is peripheral neuropathy, but this appears to be less common in children than in adults [1, 11]. Elevated hepatic transaminases are seen in about 11% and pancreatitis in 1% of adults enrolled in clinical trials of d4T. d4T has been studied in pediatric patients in combination with didanosine (ddI); no pharmacokinetic interactions were observed and there were no cases of peripheral neuropathy [12]. Lipodystrophy, and specifically lipoatrophy (loss of subcutaneous fat), are toxicities associated with the use of NRTIs, particularly d4T, in adults and children [13-15]. Among 39 children receiving d4T, lamivudine (3TC), and nelfinavir (NFV), lipodystrophy developed in 11 (28%) after a median of 49 months of therapy; 9 demonstrated lipoatrophy [16]. Further research concerning body habitus changes associated with NRTI use in pediatric patients is ongoing. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues, including d4T, alone or in combination [17, 18]. The combination of d4T and ddI in pregnant women has been associated with fatal lactic acidosis and should be used during pregnancy only if no other alternatives are available. Many of these adverse events are believed to be due to mitochondrial toxicity resulting from inhibition of mitochondrial DNA polymerase gamma, with depletion of mitochondrial DNA demonstrated in fat, muscle, peripheral blood mononuclear cells, and other tissues [17, 19-21]. (See Matrix 1 in Appendix A) While the WHO has chosen to limit the maximum dose of d4T to 30 mg (WHO guidelines [www.who.int/hiv/art/ARTAdultsaddendum.pdf]), the availability of alternatives in the United States and concerns of some Working Group members about suboptimal therapy with a lower dose support switching to another agent, rather than lowering the dose of d4T, to manage or reduce the risk of toxicity.

**Pediatric Experience**

d4T has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs [1, 3, 11, 12, 16, 22-27]. Data from multiple pediatric studies of d4T alone or in combination with other antiretrovirals demonstrate that d4T appears safe and is associated with clinical and virologic response [1, 3, 11, 12, 16, 22-25]. In HIV-infected children, d4T is commonly used as a component of a dual NRTI backbone (most often with 3TC or ddI) as part of HAART. In treatment-experienced children, the combination of d4T, NFV, and NVP was less effective in reducing plasma viral load than the combination of ddI, NFV, and ritonavir (RTV) [3]. Unfortunately, most subjects were previously treated with ZDV or d4T and viral sensitivity testing was not performed in this study. The rates of adverse events in the two groups were similar.

Many clinicians use d4T as a component of a second regimen after treatment failure or as a replacement for ZDV if the patient develops anemia. In a phase II comparison study of d4T and ZDV, they were largely comparable in terms of safety and tolerability, although neutropenia occurred significantly less often among children receiving d4T [11].

Early initiation of triple therapy with d4T, ddI, and NFV was evaluated in 20 infants starting therapy at <3 months of age (median age at initiation, 2.5 months) [25]. Therapy was generally well tolerated; 7 infants (35%) experienced 11 events considered possibly related to study drugs, although only 3 such events required drug modification (these 3 events were rash, diarrhea, and neutropenia). At least 1 episode of grade 1 hypertriglyceridemia was observed in 19 of 20 (95%) infants; 9 of 12 (75%) infants with cholesterol measured after baseline had at least 1 episode of grade 1 hypercholesterolemia. However, no infant had grade 2 or higher triglyceride or cholesterol concentrations. Seventy percent of infants had incomplete viral suppression, which was associated with genotypic resistance mutations in 6 (30%) of these infants. However, only 2 infants developed resistance mutations to d4T, and 1 of these infants had pre-existing TAMs present at baseline.

**References:**


---

**Tenofovir Disoproxil Fumarate (TDF, Viread®)**


See Also: [Appendix A: Characteristics of Available Antiretroviral Drugs](#)

**Overview**

Tenofovir disoproxil fumarate (TDF) was approved for use in combination with other antiretroviral agents for treatment of adults in October 2001. A fixed-dose combination formulation of TDF and emtricitabine (FTC) (Truvada) was approved for adults in August 2004, and a single tablet combination of TDF, FTC, and efavirenz (EFV) (Atripla) was approved for adults in July 2006. TDF is not approved for use in pediatric patients <18 years old.

Tenofovir is an acyclic nucleotide analogue with activity against retroviruses, including HIV-1, HIV-2, and hepatitis B virus. TDF, an orally active ester prodrug of tenofovir, is rapidly hydrolyzed to tenofovir by plasma esterases, then metabolized intracellularly to the active drug, tenofovir diphosphate, which competitively inhibits the HIV RT enzyme and terminates the DNA synthesis. The drug has a long half-life, allowing once daily dosing in adults, and is active against many viruses resistant to NRTIs, NNRTIs, and PIs. Oral bioavailability in adults ranges from 25% (fasting) to 39% (after a high-fat meal). TDF can be taken with or without food. TDF is excreted unchanged by the kidneys by a combination of glomerular filtration and active tubular secretion; TDF plasma clearance and exposure are related to the body weight/serum creatinine ratio (BW/SCR) [1]. The dose should be adjusted for patients with renal insufficiency. There is potential for interaction with other drugs that undergo renal excretion. There is no hepatic metabolism of TDF, and pharmacokinetics are unchanged in patients with hepatic impairment.

TDF is active against hepatitis B virus, and “flare-ups” of hepatitis B have been reported in HIV/hepatitis B coinfected patients after discontinuation of TDF therapy. Coinfected patients should be closely monitored with both clinical and laboratory follow-up for at least several months after stopping TDF treatment.

**Resistance**

While TDF is active against viral strains that are resistant to other drugs, HIV isolates with reduced susceptibility to TDF have been selected in vitro; these viruses expressed a K65R mutation in the RT gene and have a 3- to 4-fold reduction in susceptibility to TDF. The K65R mutation can also be selected in vivo in patients receiving didanosine (ddI), zalcitabine (ddC), or abacavir (ABC). Patients who develop the K65R mutation have cross-resistance to TDF, ABC, ddI, ddC, and may also show reduced susceptibility to 3TC and FTC. Combinations of tenofovir with ZDV (and to a lesser extent stavudine [d4T]) reduce the rate of selection of the K65R mutation [2]. In vitro, HIV-1 subtype C develops the K65R mutation more rapidly than subtype B [3]. Viruses containing multiple thymidine analogue mutations (e.g., mutations at RT gene codons 41 and 210, which also confer resistance to d4T, ZDV, and ABC), a mutation at codon 74 (which confers resistance to ABC, ddI, and ddC), or the T69S double insertion resistance mutation also have reduced susceptibility to TDF. In clinical studies of TDF administered as part of a triple NRTI combination in antiretroviral-naïve or-
experienced adults, early virologic non-response is common and is associated with early development of both K65R and M184V mutations [4, 5].

**Adverse Effects**

In animal studies, the principal organs affected by TDF toxicity were the renal tubular epithelium and bone. Evidence of reversible renal toxicity, including increases in serum creatinine, BUN, glycosuria, proteinuria, phosphaturia, and calcium and decreases in serum phosphate (Fanconi syndrome) have been observed in animal studies at high exposure levels; however, toxicity was not observed in infant macaques treated with low-dose TDF for 5 years [6]. Although clinically significant TDF-associated renal toxicity has been observed infrequently in prospective and retrospective clinical studies of adults [7-13], there are numerous case reports of nephrotoxicity (Fanconi syndrome, renal insufficiency, acute tubular necrosis, acute renal failure) in adults receiving TDF in combination with other drugs [7, 14-19]. There is greater risk for patients with low body weight, baseline renal insufficiency, and those using concomitant drugs that are nephrotoxic or increase the patient’s TDF exposure. Tenofovir-associated proximal renal tubular dysfunction was associated with single nucleotide polymorphism changes in the genes coding for the multidrug-resistance protein 4 transporter [20]. Discontinuation of TDF led to improvement or resolution of these clinical abnormalities. The long-term renal effects are not known. Unpublished cases of renal toxicity in adolescents taking TDF-containing regimens support the need to evaluate and monitor renal function in patients using TDF, regardless of age.

TDF caused bone toxicity (osteomalacia, growth restriction) in infant macaques when given in high doses over long periods [6]. This was reversed with dose reduction or complete discontinuation of TDF. Infant macaques receiving low daily doses of tenofovir for 5 years experienced normal growth and bone density [6]. Decreases in bone mineral density (BMD) have been shown in both adults and children taking TDF [21, 22]. The clinical significance of changes in BMD is not yet known; no increase in fracture incidence has been observed.

There is a poorly understood drug-drug interaction between TDF and ddl that results in significantly increased ddl concentrations and increased ddl toxicity. When coadministering ddl and TDF, a dose adjustment of ddl is recommended [23, 24] (the exact dose adjustment needed in children, however, is not known); patients should be monitored for symptoms of ddl toxicity, lymphopenia, and declining CD4 cell counts [14, 25, 26]. Early virologic failure has been reported with the use of TDF/ddl in combination with EFV in two adult clinical trials [27, 28]. Atazanavir (ATV) and lopinavir/ritonavir (LPV/RTV) increase TDF concentrations. The mechanism of this interaction is not known. Patients receiving ATV or LPV/r in combination with TDF should be monitored closely for TDF-associated adverse effects, and TDF should be discontinued if they occur. TDF decreases concentrations of ATV.

TDF appears less likely than other NRTI drugs to be associated with mitochondrial toxicity [29, 30]; TDF inhibits HIV RT at concentrations about 3,000-fold lower than needed to inhibit DNA polymerases beta and gamma, and is also only a weak inhibitor of the alpha, beta, and gamma DNA polymerases. In adult studies, the rate of mitochondrial side effects was 3% among TDF recipients, compared to 11% among those taking d4T [21]. However, cases of lactic acidosis have been reported with use of TDF [14, 31]. (See **Matrix 1 in Appendix A**)

In the phase I/II study of TDF in 18 children and adolescents at the National Institutes of Health (NIH), the major toxicity attributable to TDF was a >6% decrease in BMD measured by dual-energy x-ray absorptiometry (DEXA) scan in 5 of 15 (33%) children evaluated at week 48. Two of the 5 discontinued TDF at 48 weeks as required by the protocol and experienced partial or complete recovery of BMD by 96 weeks [22]. The median Tanner scores were 1 (range 1–3) and the mean age 10.2 years for the children with BMD decreases; for those whose BMD did not decrease median Tanner score was 2.5 (range 1–4) and median age was 13.2 years [22, 32]. In a second study of 6 patients at the NIH using the commercially available 300 mg formulation of TDF, 2 pre-pubertal subjects experienced >6% BMD decreases. One was the smallest child and experienced a 27% decrease, necessitating withdrawal of TDF but continuation of the rest of her ART regimen [33]. Subsequently her BMD recovered. The data from both of these small studies suggest that TDF-related bone loss may be greater in less mature children (e.g., Tanner 1–2) than in those with more advanced development (Tanner ≥3).
In contrast to the NIH studies, an Italian study showed no effect of TDF on BMD in pediatric patients who were switched from stavudine and PI-containing regimens to TDF/3TC/EFV [34]. The different results may be explained by different patient populations and TDF dosing. The patients in the study by Giacomet et al. [34] were older, had greater height and weight z scores, and the majority were in middle to late puberty or postpubertal. The NIH study involved heavily treatment experienced patients in need of salvage therapy while the Italian study evaluated BMD in a potentially healthier population who were required to have long-lasting viral suppression prior to the switch in therapy. Finally, because the patients in the Italian study received TDF in the absence of RTV and were administered fractions of TDF pills to provide lower doses, the tenofovir concentrations experienced by the Italian patients may have been lower than those seen in the NIH patients. No BMD studies have been performed in treatment-naive children who initiate therapy with TDF.

No significant renal disease was seen with TDF therapy in either of the 2 small NIH studies or in the Italian study. However, possible TDF-associated nephrotoxicity manifest as Fanconi syndrome, reduced creatinine clearance, and diabetes insipidus, has been reported in a child receiving TDF as a component of salvage therapy including LPV/RTV and ddI for 1 year [35], and increased urinary beta-2 microglobulin suggesting proximal renal tubular damage was identified in 12 of 44 (27%) children treated with tenofovir compared to 2 of 48 (4%) children not treated with tenofovir [36]. However, no significant decrease in calculated glomerular filtration rate was found in 27 HIV-infected children treated with tenofovir for 96 weeks [37]. Finally, in the Italian study, lipid profiles improved significantly after the switch from d4T and PI-containing regimens to TDF/3TC/EFV [38].

**Pediatric Experience**

In the Italian study, all HIV-infected children remained clinically stable and virologically suppressed after the change in regimen [38]. The NIH study, using a 75 mg tablet formulation of TDF in treatment-experienced children and adolescents ages 6–18 years, showed that a median dose of 208 mg per meter² of body surface area (range 161–256 mg per meter² body surface area), resulted in a median single dose AUC and C_max that were 34% and 27% lower, respectively, compared to values reported in adults administered a daily dose of 300 mg [39, 40]. Renal clearance of TDF was approximately 1.5-fold higher in children than previously reported in adults, possibly explaining the lower systemic exposure [39]. Steady state tenofovir exposures were higher but still less than those seen in adults and may reflect the concomitant treatment with ritonavir, which boosts tenofovir plasma concentrations. Lower-than anticipated tenofovir exposure was also found in young adults (median age 23 years) treated with ATV/RTV plus tenofovir [41]. The clinical impact of these low drug exposures is unknown, but in the NIH study, both single-dose and steady state AUC were associated with virologic outcome. Plasma HIV RNA concentrations (log_{10} copies/mL) decreased from a median pretreatment concentration of 5.4 log_{10} copies/mL to 4.21 log_{10} copies/mL after 48 weeks of therapy [32]. HIV RNA was <400 copies/mL in 6 subjects and <50 copies/mL in 4 subjects at 48 weeks. An investigational liquid formulation has been studied in children age 2–8 years; a TDF dose of 8 mg/kg resulted in TDF exposure similar to that observed in adults receiving a TDF 300 mg dose [42].

**References:**


---

**Zidovudine (ZDV, AZT, Retrovir®)**


See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**

Zidovudine (ZDV) was the first NRTI studied in adult and pediatric clinical trials and the first antiretroviral agent approved for treatment of HIV infection. ZDV first received FDA approval for the treatment of HIV infection in adults in 1987. It was approved for use in children ages 3 months to 12 years in May 1990. In September 1997, it was approved as a fixed combination of ZDV/lamivudine (3TC) (Combivir) for adults and adolescents >12 years old. In November 2000, it was approved as a fixed-dose combination of ZDV/3TC/abacavir (ABC) (Trizivir) for adolescents and adults weighing >40 kg. In September 2005, a generic oral formulation of ZDV was approved by the FDA for...
pediatric use; generic ZDV tablet formulations were also approved. Perinatal trial PACTG 076 established that a ZDV prophylactic regimen given during pregnancy, labor, and to the newborn reduced the risk of perinatal HIV transmission by nearly 70% [1]. ZDV received FDA approval for that indication in August 1994.

ZDV is a thymidine analogue that has its greatest activity in replicating cells. It has good CNS penetration (CSF-to-plasma concentration ratio = 0.68) and is the NRTI of choice when treating children with HIV-related CNS disease [2]. ZDV is metabolized by the liver, primarily by glucuronidation, and then excreted by the kidneys. It is well absorbed in the gut, with an average bioavailability of approximately 60%, and is approximately 35% protein bound. ZDV requires intracellular phosphorylation to become activated. The serum half-life is 1.1 hours and the intracellular half-life is 3 hours.

Resistance
The antiretroviral activity of ZDV as monotherapy is limited by emergence of resistance, which generally occurs after months to years of treatment, depending on the patient's disease stage [3]. ZDV resistance is a consequence of a stepwise accumulation of genotypic mutations in the viral reverse transcriptase (RT) enzyme, including substitutions at RT gene codons 41, 67, 70, 210, 215, and 219. Resistance mutations were shown to be present in 5 of 17 (29%) newborns born to mothers who received ZDV during pregnancy [4]. The quantity and pattern of mutations influence the level of phenotypic resistance. The codon 184 mutation associated with 3TC resistance is reported to suppress ZDV resistance in vitro; when introduced into the background of a virus containing a ZDV-resistant RT gene, this mutation suppresses the effect of some ZDV resistance mutations [5, 6]. A small proportion of patients taking ZDV may develop a multi-drug resistance genotype, leading to cross-resistance to all NRTI drugs [7].

Adverse Effects
ZDV is generally well tolerated in children; the major toxicities are macrocytic anemia and neutropenia [8]. Dose reduction and hematopoietic growth factors such as erythropoietin and filgrastim (G-CSF) have been used to mitigate these toxicities. ZDV has also been associated with reversible myopathy and cardiomyopathy. Other reported toxicities of ZDV include fatigue, headache, and nausea. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including ZDV (see Matrix 1 in Appendix A).

Pediatric Experience
ZDV has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs [2, 8-22]. Data from multiple pediatric studies of ZDV alone or in combination with other antiretrovirals demonstrate that ZDV appears safe and is associated with clinical improvement and virologic and immunologic effects [8-14]. ZDV is commonly used in HIV-infected children as a component of a dual NRTI backbone (most often with 3TC, didanosine, or ABC) used as part of HAART.

Recommended neonatal ZDV dosing for prevention of mother-to-child HIV transmission is 2 mg/kg orally every 6 hours or 1.5 mg/kg intravenously every 6 hours for those unable to receive oral dosing. Although not FDA approved, twice daily dosing (4 mg/kg every 12 hours) is sometimes prescribed when concerns about adherence exist, but the efficacy of this approach for prevention of mother-to-child transmission has not been evaluated. Pharmacokinetic studies, such as PACTG 331, have shown that dose adjustments are necessary for premature infants due to decreased ZDV clearance compared to term newborns of similar postnatal ages [15, 16].

Overall, ZDV pharmacokinetics in pediatric patients >3 months of age are similar to those in adult patients. The manufacturer’s recommended oral dose in pediatric patients 6 weeks to 12 years of age is 160 mg per meter² of body surface area every 8 hours, in combination with other antiretroviral agents, while the recommended dose for adults is 300 mg twice daily. Although not FDA approved, twice daily dosing is routinely prescribed in children receiving ZDV for treatment to improve adherence. An oral dose of 180–240 mg per meter² of body surface area twice daily in children and adolescents is recommended [9, 23]. However, pharmacokinetic data supporting twice daily dosing in children is absent.
References:


Non-Nucleoside Analogue Reverse Transcriptase Inhibitors

Efavirenz (DMP-266, EFV, SustivaTM)
URL: http://www.accessdata.fda.gov/scripts/der/dugsatfda/
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
Efavirenz (EFV) was approved in September 1998 for adults, adolescents, and children >3 years of age. Like the PIs, EFV is metabolized via the cytochrome P450 pathway (primarily CYP2B6 and CYP3A4) with polymorphic metabolism associated with CYP2B6 genotype [1, 2]. EFV has been shown to induce its own metabolism, to be an inducer of cytochrome P450 and glucuronidation isoenzymes, and also has some minimal inhibitory effects on cytochrome P450 isoenzymes. Therefore, concentrations of concomitant drugs can be decreased or less frequently increased depending on the specific enzyme pathway involved. In addition, concomitantly administered medications that induce or inhibit cytochrome P450 isoenzymes may affect the plasma concentrations of EFV. EFV is highly protein bound (>99%), and may therefore interact with other highly protein bound drugs, such as phenytoin.

Resistance
EFV, like other NNRTIs, has a low genetic barrier to resistance, with high-level resistance seen with a single mutation (lysine to asparagine), typically RT gene codon 103. Other known mutations conferring phenotypic resistance include those at codons 108, 109, 180, 214, 215, 221, 225, 228, and 230.

EFV is likely to induce its own metabolism, to be an inducer of cytochrome P450 and glucuronidation isoenzymes, and also has some minimal inhibitory effects on cytochrome P450 isoenzymes. Therefore, concentrations of concomitant drugs can be decreased or less frequently increased depending on the specific enzyme pathway involved. In addition, concomitantly administered medications that induce or inhibit cytochrome P450 isoenzymes may affect the plasma concentrations of EFV. EFV is highly protein bound (>99%), and may therefore interact with other highly protein bound drugs, such as phenytoin.

Resistance
EFV, like other NNRTIs, has a low genetic barrier to resistance, with high-level resistance seen with a single mutation (lysine to asparagine), typically RT gene codon 103. Other known mutations conferring phenotypic resistance include those at codons 108, or 225. Cross-resistance to EFV is likely with delavirdine-resistant virus and in some cases with nevirapine (NVP)-resistant virus; the extent of cross-resistance varies depending on which genotypic mutations are present.

Adverse Effects
The toxicity profile for EFV differs for adults and children. In adults, a CNS complex of confusion, agitation, sleep disturbance, nightmares, hallucinations, or other symptoms has been reported in >50% of patients [3]. These symptoms usually occur early in treatment and rarely require drug discontinuation. Bedtime dosing, particularly during the first several weeks of therapy, appears to decrease the occurrence and severity of this side effect. In some patients, the symptoms may persist or occur months after first initiating EFV. In several studies, the incidence of such side effects was correlated with EFV plasma concentrations and occurred more frequently in patients with higher concentrations [4-7]. In patients with pre-existing psychiatric conditions, EFV should be used cautiously for initial therapy. Adverse CNS effects occurred in 14% of children receiving EFV in clinical studies [8]. The principal side effect of EFV in children is rash, which was seen in up to 40% of children, compared to 27% of adults. The rash is usually maculopapular, pruritic, and mild to moderate in severity and rarely requires drug discontinuation. Onset is typically in the first 2 weeks of treatment [8]. While severe rash and Stevens-Johnson syndrome have been reported, this is rare. Other reported adverse events in adults and children include diarrhea, nausea, and increased transaminases. There are insufficient data to recommend substituting NVP for EFV following either rash or hepatotoxicity [9].

In cynomolgus monkeys, prenatal EFV exposure has been associated with congenital CNS abnormalities in infant monkeys. Based on these data and retrospective reports in humans of an unusual pattern of severe CNS defects in 4 infants after first trimester exposure to EFV-containing regimens (3 meningomyeloceles and 1 Dandy-Walker malformation), EFV has been classified as FDA Pregnancy Class D (positive evidence of human fetal risk) [10]. EFV use in the first trimester of pregnancy should be avoided, and adult and adolescent women of childbearing potential should undergo pregnancy testing as well as counseling about the risk to the fetus and the need to avoid
pregnancy before initiating EFV therapy (see Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States [11]).

**Pediatric Experience**

EFV has been studied in HIV-infected children in combination with NRTIs or with NRTIs and a PI (nelfinavir [NFV] or lopinavir/ritonavir [LPV/RTV]) [8, 12-25]. An open label study (PACTG 382) of EFV combined with NFV and 1 or 2 NRTIs was performed in 57 NNRTI- and PI-naïve pediatric patients, some as young as 3 years of age [8]. In an intent-to-treat analysis, 76% of children had plasma HIV RNA concentrations <400 copies/mL and 63% had HIV RNA concentrations <50 copies/mL at 48 weeks of therapy. The median times to achieve those concentrations were 4 and 20 weeks, respectively. Therefore, children with detectable HIV RNA (>50 copies/mL by the ultra-sensitive RNA assay) after 1 month of therapy continued to accrue some virologic benefit through 5 months of treatment with this regimen [12]. Long term virologic suppression with once daily EFV therapy in combination with FTC and ddi was reported in 37 treatment-naïve children, 3–18 years of age, participating in PACTG 1021 [23]. Eighty-five percent of subjects were able to achieve HIV-RNA <400 copies/mL and 72% maintained HIV-RNA suppression <50 copies/mL through 96 weeks of therapy.

A study of a liquid formulation of EFV in 19 HIV-infected children 3–9 years of age has been reported [13]. Studies in adult volunteers indicated that bioavailability of EFV liquid is 20% lower than that of the capsules; therefore, the initial dose of EFV liquid formulation was 20% higher than that used for EFV capsules in the earlier pediatric study (PACTG 382). The higher dose of EFV liquid formulation resulted in pharmacokinetic AUC values that were similar to those observed with EFV capsules. Antiviral effects were similar in children receiving either the liquid or the capsule EFV formulation. Pharmacokinetic data are not yet available for dosing in children <3 years of age or who weigh <13 kg. The liquid form of EFV is not yet commercially available.

Long term HIV RNA suppression has been associated with maintenance of trough EFV concentrations >1 mcg/mL in adults [7]. Early HIV RNA suppression in children has also been seen with higher drug concentrations, with EFV troughs of 1.9 mcg/mL seen in subjects with HIV RNA ≤400 copies/mL vs. EFV troughs of 1.3 mcg/mL in subjects with detectible virus (>400 copies/mL) [25]. Even with the use of FDA approved pediatric dosing, EFV concentrations can be suboptimal [26], so that some experts recommend therapeutic drug monitoring when using EFV, especially in select clinical situations such as virologic rebound or lack of response in an adherent patient.

EFV should be used with caution in adolescent women of childbearing age because of the risk for teratogenicity should EFV be taken during the first trimester, prior to recognition of pregnancy. Some clinicians may choose alternative drugs for use in sexually active adolescent women in whom contraception is erratic and the risk of unintended pregnancy is high.

**References:**


4. Zugar A. Studies disagree on frequency of late CNS side effects from efavirenz. *AIDS Clin Care*, 2006. 4(1)


Etravirine (ETR, INTELENCEᵀᴹ, TMC125)
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**
Etravirine (ETR) recently received FDA approval for use in combination with other antiretroviral agents in treatment-experienced adult patients who have resistance to efavirenz (EFV) and/or nevirapine (NVP). In patients with a history of virologic failure on an NNRTI-containing regimen, ETR should not be used in combination with only N(t)RTIs. There are insufficient data to recommend the use of ETR in pediatric patients or treatment-naïve adult patients.

ETR is an inducer of CYP3A4 and inhibitor of CYP2C9 and CYP2C19 and there are many potential drug interactions including with other ARVs. ETR should not be coadministered with other NNRTI drugs; unboosted PIs; RTV alone; or the following boosted PIs: tipranavir (TPV)/ritonavir (RTV), fosamprenavir (f-APV)/RTV, or atazanavir (ATV)/RTV.

Systemic exposure (AUC) is decreased by about 50% when taken on an empty stomach, as compared to administration following a meal. ETR should always be taken following a meal.

**Resistance**
The presence of the K103N resistance mutation associated with NVP and EFV resistance, did not affect the response rate to ETR in clinical trials. The presence at baseline of ≥3 IAS-USA-defined NNRTI substitutions results in decreased virologic response (Manufacturer’s Prescribing Info). The following baseline substitutions are associated with decreased virologic response to ETR: V179D, V179F, V179T, Y181V, and G190S.

**Adverse Effects**
The most common side effects associated with ETR include nausea and rash. Rash is generally mild to moderate, occurring primarily in the second week of therapy. Rash generally resolves after 1–2 weeks on continued therapy. Patients with a history of NNRTI-related rash do not appear to be at increased risk of developing rash with ETR. Severe rash including Stevens-Johnson syndrome, hypersensitivity reaction, and erythema multiforme occurred in <0.1% of patients during clinical trials. Treatment should be discontinued if severe rash develops.

Nevirapine (NVP, Viramune®)
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**
Nevirapine (NVP) is approved for use in children >2 months old. NVP is a dipyridodiazepinone derivative NNRTI that binds directly to the HIV-1 reverse transcriptase (RT) enzyme; RT inhibition is specific to HIV-1, and the drug has no activity against other retroviruses, including HIV-2. NVP does not inhibit any of the human cellular DNA polymerases.

NVP is highly lipophilic and widely distributed in the body; CSF- to-plasma concentration ratio is approximately 0.45. NVP undergoes extensive hepatic metabolism by way of hepatic cytochrome P450 metabolic enzymes, which NVP itself induces. During the course of the first 2 weeks of administration, plasma clearance increases as half-life decreases. NVP clearance in children is greater than in adults, and clearance in children under 9 years of age is greater than in older children [1]. Polymorphisms in the cytochrome P450 (CYP) 2B6 gene have been shown to influence NVP plasma concentrations in HIV-infected adults [2].

Due to induction of cytochrome P450 hepatic enzymes, concomitantly administered medications that induce or inhibit cytochrome P450 enzymes may affect the plasma concentration of NVP. Medications that undergo hepatic metabolism by cytochrome P450 enzymes may have concentrations increased or decreased by concomitant NVP administration.

**Resistance**
NVP has potent antiviral activity, but drug resistance develops rapidly when NVP is administered as monotherapy [3, 4]. High-level resistance has been associated with a single point mutation at codon 103, 106, 108, 181, or 188 in the RT gene, with a mutation at codon 181 being the most common [5,
Mutations associated with resistance to NVP can confer cross-resistance to other NNRTIs. HIV subtype B viruses that contain the K103N mutation as opposed to the Y181C mutation may differ in their cross-resistance to EFV [7, 8]. Viruses with the Y181C mutation alone have little resistance to EFV (although Y181C can enhance the level of resistance of viruses containing additional NVP mutations), whereas viruses with the single K103N mutation are cross-resistant to other NNRTIs [9]. Genotypic mutations associated with viral resistance to NVP typically occur within 1 to 6 weeks after initiation of NVP in situations where viral production is not effectively controlled [3, 4]. With the exception of the use of the 2-dose intrapartum/newborn NVP prophylaxis regimen to reduce perinatal HIV transmission [10], NVP should only be used in combination with other antiretroviral drugs.

**Adverse Effects**

The most common adverse events reported in adults include skin rashes, elevation of serum transaminases, headache, nausea, and fever [11-13]. In initial clinical trials of NVP treatment in HIV-infected children, rash was observed in 24% [14]. When a 2-week lower dose “lead in” period was used, the incidence of rash was decreased [1]. In a study of 4-drug therapy including NVP (given with 2 week lower dose lead in), rash was observed in only 6% of children [15]. Granulocytopenia was the second most frequent adverse event, seen in 16% of children, but it should be noted the children were also receiving zidovudine (ZDV), a known cause of granulocytopenia [1]. In a retrospective analysis of 74 children treated with NVP in the United Kingdom, 20% developed rash despite a 2-week lower dose lead in period, although some children in this study received doses higher than those currently recommended [16]. However, only 4 children required cessation of treatment due to rash. By comparison, in one antiretroviral trial of infants and young children, only 3 of 52 (6%) infants developed grade 2 or greater rash [15]. Similarly, of 57 children initiating NVP-based therapy in a program in Haiti, only 2 children developed rash requiring discontinuation of therapy [17].

Skin rash typically presents in the first 28 days after initiating therapy and in rare cases has progressed to Stevens-Johnson syndrome/toxic epidermal necrolysis, a severe skin rash accompanied by hypersensitivity reactions (characterized by rash; constitutional symptoms such as fever, arthralgia, myalgia, and lymphadenopathy; and visceral involvement such as hepatitis, eosinophilia, granulocytopenia, and renal dysfunction) or death. NVP should be permanently discontinued and not restarted if severe rash or rash with constitutional findings occurs. Most experts suggest avoidance of using EFV to substitute for NVP in patients with a history of severe rash, rash with constitutional findings, or Stevens-Johnson syndrome with NVP. However, for patients with less severe rash, EFV may be used with caution [18].

Patients experiencing rash during the 2-week lead-in period should not have their NVP dose increased until the rash has resolved. The risk of developing resistance with extended lead-in dosing is unknown and of concern and must be weighed against the patient’s overall tolerability of the regimen and the current antiviral response.

Liver function abnormalities and clinical hepatitis have been associated with NVP use. In HIV-infected adults treated with NVP, severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, have been reported (see **Matrix 1 in Appendix A**). In HIV-infected adults, risk factors for hepatic toxicity include elevated baseline serum transaminases, hepatitis B or C infection, female gender, and higher CD4 cell counts (particularly women with CD4 cell count >250 cells/mm³ and men with CD4 cell count >400 cells/mm³) [12, 13, 19]. However, serious liver dysfunction, while it can occur, appears much less common in pediatric patients receiving NVP therapy than in adults and symptomatic hepatic events have not been reported in infants or mothers receiving single dose NVP regimens for prevention of perinatal HIV infection [13].

The majority of cases of hepatic dysfunction in adults have occurred during the first 12 weeks of NVP therapy, and frequent and intensive clinical and laboratory monitoring, including liver function tests, is important during this time period. However, about one-third of cases occurred after 12 weeks of treatment, so continued periodic monitoring of liver function tests is needed. In some cases, patients presented with non-specific prodromal signs or symptoms of hepatitis and rapidly progressed to hepatic failure and, in some cases, death; patients with symptoms or signs of hepatitis should have liver function tests performed. NVP should be
permanently discontinued and not restarted in patients who develop clinical hepatitis. The safety of EFV substitution for NVP in patients who experienced NVP hepatotoxicity is unknown; EFV use in this situation has been well tolerated in the limited number (N=11) of patients that have been reported [18].

**Pediatric Experience**

NVP has been studied in HIV-infected children in combination with NRTIs or with NRTIs and a PI [1, 15, 16, 20-25]. Combination therapy with NVP, ZDV, and didanosine (ddI) in young infected infants was associated with sustained viral suppression in a small number of children [20]. A recent description of 15 infants initiating NVP-based antiretroviral treatment prior to 66 days of life in Belgium, reported that complete viral suppression (<400 copies/mL) was achieved in 11 (73%) infants [26]. A larger study, PACTG 356, treated infants and young children with 3 different NVP-containing regimens: ZDV/lamivudine (3TC)/NVP, ZDV/3TC/abacavir (ABC)/NVP, or ZDV/3TC/NVP/nelfinavir (NFV) [15]. Twenty-four percent of 17 infants treated with the 3 drug regimen had viral suppression to <400 copies/mL HIV RNA, compared with 10 of 17 (41%) and 15 of 18 (83%), respectively, of those treated with 4 drugs. Children who started therapy prior to 3 months of age had a better virologic outcome compared with those starting at an older age (3.5–24 months). PACTG 377 randomized 181 PI- and NNRTI-naïve mild-moderately immune suppressed children to 1 of 4 combination treatment regimens. All of the regimens contained stavudine (d4T) and a PI (either ritonavir [RTV] or NFV); 3 of the 4 regimens also included NVP as part of combination therapy. Children in the NVP-containing arms experienced moderate or worse skin rash more frequently than those not receiving NVP. Those children receiving a 4 drug regimen containing both NVP and a PI had a significantly greater increase in CD4 cell count from baseline to week 24 then those receiving other regimens [21]. A recent study of 212 children in Cambodia, 82% of whom received NVP and 18% EFV containing HAART, reported 156 of 212 (73.6%) having undetectable viral load (<400 copies/mL) after 12 months of treatment in an intention-to-treat analysis. Only 2 children switched regimens due to intolerability to NVP [25]. In PACTG 403, 41 children with prior NRTI experience were randomized to receive d4T/NFV/NVP or ddI/NFV/RTV. After 48 weeks of therapy, only 28% (5/18) of those still on the NVP-inclusive regimen had viral suppression to <400 copies/mL compared with 65% (11/17) of children on the RTV-based treatment. The changes in CD4% as well as the rates of toxicities were similar for both regimens. Three children developed NVP-related rashes leading to discontinuation of study treatment [24].

The efficacy of NVP-based antiretroviral therapy in infants and children previously exposed to single dose NVP (SD-NVP) for prevention of mother-to-child transmission (PMTCT) is under study. In a small, non-randomized study in Botswana, 6 month virologic and immunologic responses were compared between 15 SD-NVP exposed and 15 unexposed infants in follow-up from a PMTCT study who initiated NVP-based antiretroviral treatment at a mean age of 8 months (range 2–33 months) [27]. Only 34% of those with a history of exposure had an undetectable viral load (<400 copies/mL) compared with 91% of the unexposed cohort. CD4% was also significantly lower in the exposed group compared to the unexposed group, 23% vs. 31%, respectively. In contrast, in a study in Uganda, in which children with SD-NVP exposure started NVP-based treatment at an older age of 1.6 years, there was no difference in response to therapy between children with and without prior SD NVP exposure [28]. A large randomized clinical trial, P1060, is designed to address the impact of NVP exposure during PMTCT on the efficacy of NVP-based therapy in infants 6 months to 3 years of age.

Dosing recommendations for chronic treatment of children are somewhat controversial. Body surface area has traditionally been used to guide NVP dosing for infants and young children, with dosing recommended at 120–200 mg per meter² of body surface area every 12 hours, at a maximum of 200 mg per dose. Younger children (e.g., age <8 years) may require the higher range of dosage (i.e., 200 mg per meter² of body surface area twice daily) [20, 22]. The drug label also includes dosing recommendations based on mg/kg dosing. NVP apparent clearance adjusted for body weight is approximately 2-fold greater in children <8 years of age; however, these clearance changes are gradual and the mg/kg dosing recommendations result in an abrupt 43% decrease in dose size when the 8th birthday is reached. Therefore, the mg per m² of body surface area dosing calculation that was used in clinical trials is recommended for dosing of NVP in...
children, rather than the FDA-recommended mg/kg dosing regimen [29].

References:


Protease Inhibitors

**Atazanavir (ATV, ReyatazTM)**


See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**

Atazanavir (ATV) was approved in June 2003 for treatment of HIV infection in individuals >16 years of age. The recommended adult dose is 400 mg, once a day, for treatment naïve adults, and 300 mg with 100 mg ritonavir (RTV), for treatment experienced individuals [1]. Safety and effectiveness of ATV in pediatric patients is under study, but an appropriate dosage has not yet been determined. Unboosted and RTV-boosted ATV is currently being studied in an ongoing trial in children and adolescents to age 21.

ATV is an azapeptide aspartyl PI that differs structurally from other approved peptidomimetic PIs (C-2 symmetric chemical structure). ATV is rapidly absorbed following oral administration, and should be administered with food to increase bioavailability and reduce pharmacokinetic variability.

Administration with a light meal resulted in a 70% increase in systemic ATV exposure (AUC) and a 57% increase in peak concentrations relative to the fasting state, and administration with a high-fat meal resulted in a mean increase in AUC of 35% and no change in peak concentrations relative to the fasting state. Gastric acid suppression (antacids, H2 blockers, proton-pump inhibitors, etc.) reduces the bioavailability of ATV [2]. Current recommendations are to avoid proton-pump inhibitors and to separate histamine-2 blockers by 12 hours from ATV dosing [1, 3]. However, four reports document success of RTV-boosted ATV in maintaining HIV viral suppression in patients receiving proton pump inhibitors [4-7]. ATV is extensively metabolized via the hepatic CYP3A enzyme pathway, and is primarily excreted in the feces in the form of metabolites. The median half-life in adults is 6.5 hours, allowing once daily administration. Passage into CSF is limited; in a multiple-dose study in HIV-infected patients, the CSF-to-plasma ratio for ATV ranged between 0.0021–0.0026. ATV is a potent inhibitor of the energy-dependent adenosine triphosphate-binding cassette drug efflux pumps (e.g., P-glycoprotein and multidrug resistance [MDR]-associated protein)
resulting in reduced efflux of PIs and certain chemotherapeutic agents. When ATV is used in combination with other PIs or certain chemotherapeutic agents, the results are higher intracellular concentrations of each [8].

Resistance
Like other PIs, several mutations are generally required to result in clinically significant drug resistance [9]. ATV has a unique resistance profile. Treatment-naïve patients developed a characteristic I50L mutation that is associated with increased susceptibility to other PIs; however, the clinical significance of this finding is unknown [10]. The I50L mutation is frequently detected in tandem with the A71V substitution that helps restore viability and increases atazanavir resistance [10]. In contrast, treatment-experienced patients did not develop the I50L mutation; rather, these patients developed mutations (M46L, A71V/T, I84V, N88S/D, and L90M) that reduced response to ATV and conferred high level cross-resistance to other PIs. Generally, if there were pre-existing PI mutations in the patient’s virus population prior to ATV initiation, ATV resistance developed through mutations associated with resistance to other PIs, instead of through the I50L mutation. While HIV isolates resistant to only 1 or 2 PIs may remain sensitive to ATV, cross-resistance with ATV increases as isolates exhibit increasing resistance to multiple PIs. For treatment experienced pediatric patients, baseline resistance assays that revealed mutations at any of codons 13, 54, 73, or 84 were associated with loss of sensitivity (>2.5) on phenotypic assay testing. In addition, the presence of ≥7 PI mutations was associated with a ≥10-fold loss of sensitivity.

Adverse Effects
The most common side effects associated with ATV include gastrointestinal symptoms (e.g., nausea, vomiting, abdominal pain, diarrhea), scleral icteris and/or mild jaundice, headache, rash, tingling in hands and feet, and depression. In a report from France, urolithiasis and/or kidney stones, has been reported in 1% of adult patients treated with ATV containing regimens [11]. Unlike other PIs, ATV does not appear to be associated with an increase in total cholesterol, LDL cholesterol, or triglycerides [12]. Switching adult patients with severe hyperlipidemia to an ATV-containing regimen from one with other PIs resulted in improvements in atherogenic lipid profiles [13]. As with other PIs, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur.

ATV inhibits the hepatic glucuronidation enzyme uridine diphosphate glucuronosyl transferase (UGT1A1) that conjugates bilirubin. ATV administration is frequently associated with asymptomatic indirect hyperbilirubinemia, which may be accompanied by scleral icterus or visible jaundice. This is not accompanied by elevations in hepatic transaminases, but may be cosmetically disturbing. The degree of hyperbilirubinemia correlates directly with the atazanavir plasma concentration (not intracellular concentration) [14]. One of the factors that impacts the ATV plasma concentration and the ATV-related hyperbilirubinemia is the MDR1 genotype. Individuals who have polymorphisms at MDR1 position 3435 (CT or TT) are more likely to have lower ATV plasma concentrations and lower bilirubin concentrations than individuals with wild-type genotype at 3435 (CC) [15]. The jaundice is reversible following discontinuation of ATV therapy. ATV has been reported to prolong the PR interval of the electrocardiogram. In the majority of patients, abnormalities in atrio-ventricular (AV) conduction were asymptomatic and limited to first-degree AV block; no second or third degree AV block has been observed. However, because experience with ATV is limited, caution should be exercised when ATV is used in patients with pre-existing conduction system disease or those receiving other drugs that prolong the PR interval (e.g., most beta-blockers, digoxin, verapamil).

ATV is principally metabolized by the liver, and individuals with hepatic impairment may have increased ATV concentrations. Individuals with hepatitis B or C infections or marked elevations in transaminases prior to treatment may be at increased risk for further elevations in transaminases or hepatic decompensation.

Pediatric Experience
ATV is not currently approved for use in children, but clinical trials are underway. Unboosted and RTV-boosted ATV is currently being studied in an ongoing trial in children and adolescents to age 21. Studies to date indicate that if unboosted ATV is used, higher doses (on a per kg or m2 basis) are required to achieve adequate drug levels. For older adolescents, doses employed in these studies have been above the adult approved dose of 400 mg once
ATV, in combination with NRTIs with and without low-dose RTV boosting, has been studied in HIV-infected children 3 months to 21 years of age in a phase II study, PACTG 1020A [16, 17]. In addition to capsules, a powder formulation is also being evaluated. These pediatric dose-finding trials are using ATV plasma concentration monitoring to guide therapy. When using the ATV capsule formulation, without RTV, results suggest children ≥5 years of age require ATV dosing of 520–620 mg per meter² of body surface area per day compared to an ATV dose of 205 mg per meter² of body surface area per day when used in combination with RTV. The AUC were similar in the two groups, though the Cmax were higher and Cmin lower on the unboosted arms. Seventy-nine percent of treatment-naïve patients had HIV RNA <400 copies/mL at week 24; 43% of treatment-experienced patients had HIV RNA <400 copies/mL at week 24. Eleven of 129 (8.5%) patients enrolled had a bilirubin >5 times the upper limit of normal. Asymptomatic electrocardiogram (EKG) abnormalities were observed in a small number of patients: 1 patient had a grade 3 QTC prolongation, 9 had grade 2 PR or HR changes, 3 subjects had grade 3 PR prolongations. No significant changes in serum cholesterol or triglycerides were observed during 48 weeks of therapy in 63 children receiving ATV in combination with 2 NRTIs [17].

Current recommendations for HIV-infected adults include the use of unboosted ATV only in treatment-naïve patients. All treatment-experienced patients should receive RTV-boosted ATV therapy. Decreased ATV exposure (increased clearance) has been observed when coadministered with efavirenz, nevirapine, and tenofovir disoproxil fumarate [18]; coadministration of ATV with low-dose RTV boosting is recommended if ATV is administered with either of these drugs. Administration of ATV with RTV-boosted lopinavir results in decreased plasma concentrations of lopinavir. No dose adjustment is required [19]. Administration of ATV with fosamprenavir (f-APV) results in significantly lower concentrations of ATV [3, 20]. ATV boosting with RTV may be necessary to ensure adequate ATV concentrations when administering ATV with f-APV.

References:
Darunavir (DRV, Prezista®)

URL: http://www.accessdata.fda.gov/scripts/cder/drgsatfda/
See also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
Darunavir ethanolate (DRV) is a non-peptidic PI developed because of its extreme potency against multidrug-resistant strains of HIV. It was FDA approved in 2006, for use in treatment-experienced adult patients likely to have resistance to >1 PI. The likelihood of treatment response with DRV is greater when the drug is used in combination with other active drugs. To achieve optimal effect, DRV must be taken with food and coadministered with ritonavir (RTV).

DRV has activity against HIV-1 group M and group O isolates and against laboratory strains of HIV-2. Median EC_{50} values range from 0.7–5.0 ng/mL, and human serum increases EC_{50} by a median factor of 5.4-fold (i.e., protein binding has an effect on the EC_{50}). The protein-binding-adjusted EC_{90} for wild-type virus is 200 ng/mL, and the protein-binding-adjusted EC_{50} for resistant virus is 550 ng/mL.

Resistance
In patients previously treated with PIs who were treated with DRV and then had virological failure, protease resistance mutations at amino acid position V32I occurred in 30%, substitutions at I54 developed in >20%, and substitutions at I15, L33, I47, G73, and L89 occurred in 10%–20%. For these patients who developed resistance on therapy, the median phenotype fold change resistance at baseline was 21-fold, and at failure was 94-fold. Reduced control of plasma viral load is seen in patients with >7-fold change resistance at baseline.

DRV has <10-fold decreased susceptibility in cell culture against 90% of 3,309 isolates resistant to amprenavir (APV), atazanavir (ATV), indinavir (IDV), lopinavir (LPV), nelfinavir (NFV), RTV, saquinavir (SQV), and/or tipranavir (TPV), showing that viruses resistant to these PIs remained susceptible to DRV. However, DRV-resistant viruses are also resistant to APV, ATV, IDV, LPV, NFV, RTV, and SQV. Some DRV-resistant viruses maintain susceptibility to TPV.

Adverse Effects
The most common adverse events related to treatment in early trials were diarrhea, nausea,
headache, and nasopharyngitis. Skin rash occurred in 7% of subjects treated with DRV in its early development. These rashes were generally mild to moderate, self-limited, maculopapular eruptions, but severe skin rash, including erythema multiforme and Stevens-Johnson syndrome, have been reported, and discontinuation due to rash occurred in 0.3%. In some cases, fever and elevation of transaminases were reported in combination with rash. Increased plasma lipids and increase in amylase were also seen in early studies.

There are many drug interactions (see Matrices 2-4 in Appendix A). The drug is metabolized by CYP3A4, and may increase or decrease the metabolism of many other agents, including other PIs and NNRTIs. Refer to the product label before prescribing, especially in combination with other antiretrovirals.

Pediatric Experience
There are no published data concerning DRV use in children. A study to measure drug pharmacokinetics in children is ongoing. In adults, a dose of DRV 600 mg and RTV 100 mg given twice daily results in a median AUC of 61,668 ng*h/mL (range 33,857–106,490 ng*h/mL) and median predose plasma concentration of 3,539 ng/mL (range 1,255–7,368 ng/mL).

References:

Fosamprenavir (f-APV, Lexiva™)
URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
In October 2003, fosamprenavir calcium (f-APV), a prodrug of amprenavir (APV), was approved for use in combination with other antiretrovirals for the treatment of HIV infection in adults. This approval was based on results from two studies in antiretroviral naïve adults and one study in PI-experienced adults. In June 2007, the f-APV solution was approved and indications for pediatric patients provided.

The prodrug f-APV is rapidly and almost completely hydrolyzed to APV by cellular phosphatases in the gut as it is absorbed [1, 2]. The tablet formulation of the drug can be administered with or without food without any significant effects on pharmacokinetic parameters. Peak APV serum concentrations are reached between 1.5–4 hours (mean 2.5 hours). Approximately 90% of APV is plasma protein bound, primarily by alpha 1-acid glycoprotein (AAG). APV is extensively metabolized by cytochrome P450 isoenzyme CYP3A4; there is potential for multiple drug interactions (see Matrices 1-4 in Appendix A). Ritonavir (RTV) inhibits the metabolism of APV, resulting in increases in both AUC and trough drug concentrations of APV. Unlike APV, the f-APV formulation contains no vitamin E. Dose reductions of f-APV are necessary in patients with hepatic impairment.

Resistance
Genotypic analysis of isolates from APV-treated patients shows that mutations are induced in the HIV protease gene at codons 32, 46, 47, 50, 54, 84, and at the p1/p6 cleavage site. At least 2–3 mutations are required at amino acid residues 46, 47, and 50 to produce >10-fold decrease in sensitivity. Varying degrees of cross-resistance among HIV-1 PIs have been observed.

Adverse Effects
f-APV is generally well tolerated. The most common side effects associated with f-APV include gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea), perioral paresthesias, headache, and rash. When compared to nelfinavir, there is a lower rate of gastrointestinal adverse effects. Although rash was reported in approximately 19% of patients in the efficacy trials, life-threatening rash, including Stevens-Johnson syndrome, are rare, reported in <1% of patients taking the parent compound, APV [3, 4]. f-APV should be discontinued for severe rash, including Steven-Johnson syndrome or moderate rash with systemic symptoms. APV is related to the sulfonamides, and the potential for cross-sensitivity of sulfonamides and APV is unknown. f-APV should therefore be used with caution in patients with a history of sulfonamide allergy. Fat redistribution and lipid abnormalities have been reported with the use of f-APV. As with other PIs, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and spontaneous bleeding in hemophiliacs may occur. Hemolytic anemia and elevation in serum transaminases are also reported, rare, adverse events.
Pediatric Experience

In June 2007, f-APV suspension was approved for use in pediatric patients. The approval was based on two open label studies in pediatric patients between 2–18 years of age [5, 6]. Both studies enrolled treatment-experienced and treatment-naive subjects. In one study, twice-daily dosing regimens (with or without RTV) were evaluated in combination with other antiretroviral agents. Overall, f-APV was well tolerated and effective in suppressing viral load and increasing CD4 cell count. In the APV 29005 trial after 24 weeks, 67% of PI-naive subjects in the f-APV group (age 2–5 years only), and 70% in the f-APV + RTV group achieved HIV RNA <400 copies/mL, 57% of PI-experienced subjects in the f-APV + RTV group. Median increases in CD4% at week 24 occurred in all groups, and ranged from 4%–8% [5]. In the APV 20003 trial, once daily f-APV + RTV was studied. Following information about suboptimal response to once daily dosing in treatment-experienced adults, pediatric patients were allowed to switch to twice daily therapy. Few patients opted to switch therapy and HIV RNA <400 copies/mL among PI-naive and -experienced subjects at weeks 24 and 48 were 66% and 47% and 57% and 43%, respectively. Median increase in CD4% at week 48 was 10% for PI-naive and 5% for PI-experienced subjects [6]. These data were insufficient to support a once-daily dosing regimen of RTV-boosted f-APV in pediatric patients. Toxicities from these trials included vomiting (3%–7%), diarrhea (3%–4%), and nausea (3%–4%).

The approved adolescent/adult dosing regimen depends on whether the patient is antiretroviral naïve or experienced. Only antiretroviral-naive patients should receive unboosted f-APV or once daily therapy. PI-experienced patients should receive the RTV-boosted twice daily regimen.

References:

Indinavir (IDV, Crixivan®)
URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
Indinavir (IDV) was approved in 1996 for use in adults and adolescents >18 years. Like the other PIs, IDV is prone to multiple drug interactions due to its interaction with the cytochrome P450 system (see product label). A liquid formulation is not available. Administration of IDV with a meal high in calories, fat, and protein results in a reduction in plasma IDV concentrations. Administration on an empty stomach 1 hour before or 2 hours after a meal, or with a light meal (e.g., dry toast with jelly, apple juice, and coffee with skim milk and sugar) results in little to no change in IDV pharmacokinetics. When given in combination with ritonavir (RTV), meal restrictions are no longer necessary. Decreased IDV exposure over time in children maintained on relatively fixed doses of IDV are associated with virological failure.
This may be prevented by frequent dosage adjustment and therapeutic drug monitoring, when possible \cite{1}.

\textbf{Resistance}

Resistance to IDV is associated with mutations at codons 24, 32, 46, 53, 72, 82, 84, and 90. Virus resistant to IDV may also be resistant to RTV.

Resistance to IDV/RTV combination therapy is associated with mutations at codons 10, 20, 24, 32, 36, 46, 54, 71, 73, 76, 77, 82, 84, and 90. Major mutations are located at codons 46, 82, and 84 \cite{2}. IDV-resistant virus may be broadly cross-resistant to all other PIs.

\textbf{Adverse Effects}

The most serious side effect observed in both adults and children treated with IDV is nephrolithiasis. In double-blind clinical trials in adults, the incidence of nephrolithiasis was 9.3% in IDV-containing treatment groups. Abnormal renal function (including acute renal failure) has been observed in a small number of patients with nephrolithiasis; abnormal renal function was generally transient and temporarily related to the acute episode. Interstitial nephritis has also been observed in patients receiving IDV. If signs and symptoms such as flank pain with or without hematuria occur, temporary interruption of therapy (for 1 to 3 days) during the acute episode may be considered. Adequate hydration is essential when IDV is administered. The cumulative frequency of nephrolithiasis is substantially higher in children (29%) than in adults (12.4%, range across clinical trials 4.7%–34.4%) \cite{3}. This is likely due to the difficulty in maintaining adequate hydration in children. In an IDV study in 54 children, 13% developed hematuria \cite{4}. Children treated with IDV also have a high cumulative incidence of sterile leukocyturia, which may be accompanied by elevations in serum creatinine in the absence of clinical symptoms of nephrolithiasis \cite{5}.

Asymptomatic mild elevation of bilirubin, due to an increase in indirect bilirubin, has also been reported in adults and children receiving IDV. In adult trials, about 10% of IDV-receiving patients had bilirubin values ≥2.5 mg/dL at some point during treatment; in most cases, the maximum bilirubin elevations were observed after ≥1 weeks of treatment. Clinical adverse effects such as jaundice or elevations in serum transaminases have only rarely been reported. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis have been reported.

\textbf{Pediatric Experience}

IDV has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs \cite{1, 4-18}. IDV has been studied in mostly small, uncontrolled pediatric trials, but has not been FDA-approved in the pediatric age group. IDV has been administered in dosage ranges of 300–600 mg per meter\textsuperscript{2} of body surface area given every 8 hours, and RTV-boosted IDV has been administered in IDV/RTV doses of 500/100 or 400/125 mg per meter\textsuperscript{2} twice daily \cite{4, 6-9, 11, 13-15, 18}. Virologic, immunologic, and clinical response to IDV-based therapy in children has been observed in several small studies. In an open label study in 28 children receiving IDV/zidovudine (ZDV)/lamivudine (3TC), 70% of children had HIV RNA concentrations of <500 copies/mL after 6 months of therapy \cite{13}. In an open label study of IDV/stavudine (d4T)/3TC treatment in 25 Italian children, HIV RNA concentrations were maintained at <400 copies/mL after 18 months of therapy in 87% of children who entered the study with CD4 cell counts in CDC Immune Class 2 and 72% of those who entered with CDC Immune Class 3 \cite{14}. In a study in 33 infected children who had received ≥96 weeks of treatment with IDV/ZDV/3TC (with an initial 16 weeks of IDV monotherapy), a median increase in CD4 cell count of 199 cells/mm\textsuperscript{3} and a median decrease in HIV RNA of 0.74 log was observed at 96 weeks \cite{10}. Virologic response in this study may have been impacted by the prolonged period of IDV monotherapy prior to combination with ZDV/3TC. In one study of 24 children receiving a regimen of IDV, ZDV, and 3TC, virologic responders showed significant increases in height and weight, but the virologic non-responders did not \cite{16}. In another study of 21 children receiving PI-containing antiretroviral therapy, all patients receiving IDV experienced substantial increases in their triglyceride concentrations, but no significant increases in total cholesterol occurred; blood glucose concentrations were not significantly different between baseline and follow-up evaluations \cite{19}. A multicenter, randomized clinical trial studying RTV in combination with nucleoside analogues in children was altered because of an unanticipated unavailability of RTV capsules. Children were given the option of continuing the trial with their treatment including a switch from RTV capsules to either RTV liquid or IDV capsules with a continuation of their nucleoside analogue therapy. A
matched pairs analysis of 25 children aged 2–17 years of age who were switched to IDV (600 mg per meter² every 8 hours) and 25 children who continued to receive RTV in liquid form was performed. Pharmacokinetic studies of IDV were done on 6 children at 1 and 3 weeks of treatment. Although there was no difference in oral clearance of IDV, the median trough concentrations were low and the elimination half life decreased significantly. There were no significant differences between the groups over a 24 week observation period with regard to median CD4 counts over time and number of children with HIV RNA ≤200 copies/mL. Toxicities observed with IDV included flank pain and headache (16%), renal dysfunction (16%), hematuria (12%), and skin rash (12%) [18].

Data in children indicate that a pediatric dose of 500–600 mg IDV per meter² of body surface area given every 8 hours results in peak values similar to those in adults; however, there was a significant proportion of children whose trough IDV values were less than the 0.1 mg/L value associated with virologic efficacy in adults [7, 18]. The more frequent incidence of renal toxicity in children than in adults has precluded studying higher doses of IDV [4, 5]. Therefore, two small studies have evaluated IDV in combination with low-dose RTV boosting in children. One study evaluated 500 mg IDV per meter² of body surface area plus 100 mg RTV per meter² of body surface area twice daily in 4 children aged 1–10 years; in one child, this resulted in high concentrations of both drugs and was accompanied by symptoms of renal toxicity [12]. The other study evaluated the pharmacokinetics of 400 mg IDV per meter² of body surface area plus 125 mg RTV per meter² of body surface area twice daily in 14 children; this dosing resulted in AUC and trough concentrations similar to those observed with standard doses of IDV/RTV in adults (800 mg IDV/100 mg RTV twice daily), although the peak concentration was slightly decreased [17]. Clinical results from that trial demonstrated that virologic efficacy was good but that 4 of 21 patients developed nephrolithiasis and the overall rate of side effects and intolerance to the regimen was high [8].

References:


### Lopinavir/Ritonavir (LPV/RTV, Kaletra)


**See Also:** Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**

Lopinavir/ritonavir (LPV/RTV) is a fixed combination of 2 PIs. LPV/RTV received FDA approval in 2000 for use in combination with other antiretroviral agents for the treatment of HIV-1 infection in adults and pediatric patients age 6 months and older. It is available in both liquid and capsule formulations. The liquid formulation contains 80 mg LPV/20 mg RTV per mL. A new tablet formulation (200 mg LPV/50 mg RTV) was approved in October 2005 and a pediatric version (100 mg LPV/25 mg RTV) was approved in November 2007; these new tablet formulations do not require refrigeration and can be administered without regard to food. Capsule formulation of 133.3 mg LPV/33.3 mg RTV is no longer available in the United States.

Like other PIs, LPV/RTV is metabolized by the hepatic cytochrome P450 system and multiple drug interactions are possible (see product label). Administration of LPV/RTV with food increases plasma concentrations; to enhance bioavailability and minimize pharmacokinetic variability, LPV/RTV capsules and oral solution should be taken with food; LPV/RTV tablets can be administered without regard to food.

Recently, the FDA approved the use of LPV/RTV 800/200 mg once daily administration for the treatment of HIV infection in therapy-naïve adults >18 years of age. However, once daily administration cannot be recommended for use in children in the absence of therapeutic drug monitoring because of high inter-individual variability in drug exposure and trough plasma concentrations below the therapeutic range for wild-type virus in 3/7 (43%) [1] and 10/19 (53%) [2] children treated with once daily administration. Therapy-experienced patients should only receive the twice daily regimen because trough concentrations are significantly lower with once daily administration, and there are no clinical trials comparing the two dosages in these patients. LPV/RTV should not be administered once daily in combination with efavirenz (EFV), nevirapine (NVP), amprenavir (APV), nelfinavir (NFV), or other medications that could potentially further reduce LPV concentrations.
Resistance to LPV/RTV has been associated with the accumulation of specific mutations in the protease enzyme; when compared to LPV susceptibility in wild type HIV-1, >5-fold LPV resistance is found in the presence of≥1 primary mutations at protease amino acid positions 32, 47, 48, 50, 82, or 84 when that mutation is combined with 3 or more secondary mutations at protease positions 10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 53, 54, 71, 73, 77, 82, 84, or 90.[3, 4] In one study, virologic response to therapy, measured as HIV RNA <50 copies/mL at 48 weeks, was associated with LPV susceptibility at the start of treatment, and virologic response rates of 81%, 60%, and 25% were associated with baseline LPV phenotype susceptibility (defined as the fold-change in susceptibility compared to wild type HIV-1) of<10-fold, >10- to <40-fold, and >40-fold, respectively.[4] Similarly, treatment response was 83% and 52% when the number of baseline protease mutations was ≤5 or >5, respectively. In 56 children with prior antiretroviral therapy (most with ≥3 antiretroviral regimen changes in the past), response to LPV/RTV-containing salvage therapy was poor when pre-therapy resistance profiles showed ≥6 of the mutations listed above, and was especially poor in those patients with mutations at positions 54 and 82.[5]

More important than resistance alone is the relationship of the drug exposure (trough plasma concentration measured just prior to a dose, or \(C_{\text{trough}}\)) to the susceptibility of the HIV-1 isolate (50% effective concentration, or \(EC_{50}\)). The ratio of \(C_{\text{trough}}\) to \(EC_{50}\) is called the inhibitory quotient, and in both adults and children treated with LPV/RTV, virus load reduction is more closely associated with inhibitory quotient than with either the \(C_{\text{trough}}\) or \(EC_{50}\) alone.[6-9] Cross-resistance among PIs can occur. In patients failing therapy with LPV/RTV, detection of LPV resistance is more likely in patients with prior PI treatment compared to patients not previously treated with PIs.

Adverse Effects

The most common side effects associated with LPV/RTV have been diarrhea, asthenia, and triglyceride and cholesterol elevations. Pancreatitis has been reported in adult patients taking LPV/RTV. High triglyceride concentrations may be a risk factor for pancreatitis. As with all PI drugs, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis may occur.

Pediatric Experience

LPV/RTV has been studied in HIV-infected children in combination with NRTIs and NNRTIs.[8, 10-22] RTV acts as a pharmacokinetic enhancer by inhibiting the metabolism of LPV and therefore increasing its plasma concentration. LPV/RTV is the first coformulated drug available for children.

Abbott Laboratories Study M98-940 was a phase I/II open label study that evaluated the pharmacokinetic profile, tolerability, safety, and efficacy of LPV/RTV oral solution and either 2 NRTIs or NVP plus up to 2 NRTIs in 100 pediatric patients. Through 48 weeks of therapy, the proportion of patients with HIV RNA <400 copies/mL was 37 of 44 (84%) for antiretroviral-naïve patients and 42 of 56 (75%) for antiretroviral-experienced patients. The mean increase from baseline in CD4 cell count was 404 cells/mm³ for antiretroviral-naïve and 284 cells/mm³ for antiretroviral-experienced patients treated through 48 weeks. In patients with HIV RNA >400 copies/mL at 24 or 48 weeks, there were no detectable changes in phenotypic susceptibility to LPV compared to baseline isolates, although there were resistance mutations to NRTIs and NNRTIs identified in the rebound isolates.[23]

LPV/RTV has been shown to be effective as salvage therapy in children with HIV and severe immune suppression.[13, 24], although patients with greater prior exposure to antiretrovirals may have slower reductions in virus load to undetectable concentrations.[24] In an observational cohort study in 4 Spanish hospitals analyzing salvage therapy for children with HIV, 20 children treated with LPV/RTV were 8 times more likely to reduce plasma virus load to <400 copies/mL than 15 children treated with NFV.[16].

There is still some controversy about dosing of LPV/RTV in children. Children have much lower drug exposure than adults when treated with doses that are directly scaled for body surface area. The “directly scaled” dose approximation of the adult dose in children can be calculated by dividing the adult dose by the usual adult body surface area of 1.73 meter². This suggests that for the adult dose of 400 mg LPV/100 mg RTV, the appropriate pediatric dose would be approximately 230 mg LPV/57.5 mg RTV per meter² of body surface area. However,
younger children have enhanced LPV clearance, and may need higher drug doses to achieve drug exposures similar to those in adults treated with standard doses. Additionally, a dose that results in a pediatric AUC similar to the AUC in adults is likely to be associated with a pediatric $C_{\text{trough}}$ that is lower than that found in adults.

For 12 children ages 6 months to 12 years receiving 230 mg LPV/57.5 mg RTV per meter$^2$ of body surface area twice daily (without NVP), the mean $C_{\text{trough}}$ was 4.74 ± 2.93 mcg/mL (about 67% of the adult value, which was 7.1 ± 2.9 mcg/mL) [10]. To achieve similar $C_{\text{trough}}$ to that observed in adults at the standard dose, the pediatric dose would need to be increased 30% over the directly body surface area-scaled dose. In the same study for 15 children ages 6 months to 12 years treated with 300 mg LPV/75 mg RTV per meter$^2$ of body surface area twice daily (without NVP), the mean $C_{\text{trough}}$ was 7.91 ± 4.52 mcg/mL, similar to that in adults treated with 400 mg LPV/100 mg RTV kg twice daily [10].

Since age is associated with LPV clearance (and hence AUC and $C_{\text{trough}}$), the appropriate LPV/RTV dose varies with the age of the patient treated. Children treated with approved doses will likely have trough concentrations lower than those found in adults, although virologic efficacy does not appear to be compromised. AUC similar to those seen in adults are achieved by higher doses of LPV/RTV; therefore, some clinicians may choose to initiate therapy with the following dosing scheme:

- Age 6 weeks to <6 months: 300 mg LPV/57.5 mg RTV per meter$^2$ of body surface area twice daily (without NVP) [20];
- Age 6 months to <2 years: 300 mg LPV/57.5 mg RTV per meter$^2$ of body surface area twice daily (without NVP) [18];
- Age 2 years to 12 years: 230 mg LPV/57.5 mg RTV per meter$^2$ of body surface area twice daily (without NVP) [23].

For children <6 weeks of age, even the dose of 300 mg LPV/75 mg RTV per meter$^2$ of body surface area twice daily (without NVP) results in lower drug exposures compared to those found in older infants and children [21].

For children, as in adults, the LPV $C_{\text{trough}}$ is further reduced by concurrent treatment with NNRTIs; in 14 children treated with 230 mg LPV/57.5 mg RTV per meter$^2$ of body surface area twice daily plus nevirapine (NVP), the mean $C_{\text{trough}}$ was 3.77 ± 3.57 mcg/mL [10]. For 12 children treated with 300 mg LPV/75 mg RTV per meter$^2$ of body surface area twice daily, the mean $C_{\text{trough}}$ was 5.62 ± 3.32 mcg/mL. Not only are these trough plasma concentrations lower than those found in adults treated with standard doses of LPV/RTV, the variability in concentration is much higher in children than adults [10, 18]. In a study of 15 children with HIV infection treated with the combination of LPV/RTV using an increased dose of 300 mg LPV/75 mg RTV per meter$^2$ of body surface area twice daily plus EFV 14 mg/kg/dose once daily, the median 12-hour LPV trough was 5.7 mcg/mL, but there was 34-fold inter-individual variation in LPV trough concentrations, and 5 of 15 (33%) children had LPV 12-hour trough concentrations <1.0 mcg/mL, the plasma concentration needed to inhibit wild-type HIV. The 5 children with the lowest plasma concentrations of LPV were of African origin; however, 4 of the remaining 10 children were also of African origin [11].

A pilot observational study using the inhibitory quotient (the ratio of $C_{\text{trough}}$ to EC$_{50}$) to guide therapy and evaluate the benefit and safety of higher doses of LPV/RTV in 12 children failing prior antiretroviral therapy has been conducted [8]. A study of the practical application of the inhibitory quotient to guide therapy and using the higher doses of LPV/RTV in children and adolescents suggests this approach might be applicable to patients with moderately reduced susceptibility to LPV, and show the safety and tolerability of doses of 400 mg LPV/75 mg RTV per meter$^2$ of body surface area twice daily (without NVP or EFV) and 480 mg LPV/100 mg RTV per meter$^2$ of body surface area twice daily (with NVP or EFV) [22].

References:


Nelfinavir (NFV, Viracept)
URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview
There is extensive pediatric experience with NFV-based regimens in antiretroviral-naive and -experienced children, with follow-up data in children receiving NFV for as long as 7 years [1]. NFV was approved in March 1997 and is approved for use in children >2 years of age in combination with NRTIs and NNRTIs. It is available in both oral powder and tablet formulations. NFV is active against both HIV-1 and HIV-2 strains. Exposure to NFV is significantly increased by administration with food, especially a high fat meal. Because of the large food effect seen with NFV administration, variations in plasma concentrations are likely to occur. Like other PIs, NFV is metabolized by the cytochrome P450 enzyme system in the liver, inhibits CYP3A4, and is associated with a number of clinically significant pharmacologic drug interactions.

Resistance
NFV-resistant virus contains a unique protease enzyme mutation at codon 30, which alone does not confer cross-resistance to other PIs, but does result in reduced replication capacity of the HIV isolate [2]. In adults, the mutation at position 30 occurs in approximately 30% of patients with virologic failure, while a mutation at amino acid 90 occurs in only about 5% [3]. Since the mutation at position 30 does not lead to cross-resistance to other PIs (unlike the mutation at position 90), some have suggested that NFV may be a good choice for use as the first PI in adults, since virologic failure accompanied by mutation at position 30 may not constrain future PI choice. However, in children failing NFV in their first PI-containing regimen, the mutation at position 30 occurred in 30% (similar to that in adults), but the mutation at position 90 was also relatively frequent, occurring in 24% of the 41 patients studied [4]. In a study among African children in Cote d’Ivoire where CRF02-AG strains of HIV-1 predominate, the 90M, 46L, 88S, or 54V mutations were found in 11 (38%) of the 29 children receiving NFV but the D30N was not detected [5]. The continued use of NFV in the presence of viremia may result in the selection of additional mutations in the protease gene at amino acid positions 30, 35, 36, 46, 48, 71, 77, 82, 84, 88, and 90, which leads to decreased susceptibility to other PIs. While changing from NFV to another PI may be effective if the mutation at position 90 or multiple other PI mutations have not developed, changing to NFV from another PI is less likely to be effective, since mutations selected for by other PIs confer high-level cross-resistance to NFV [6].

Adverse Effects
NFV has been relatively well tolerated in children, even when dosing schemes exceed adult recommended amounts. The most common adverse effects include diarrhea, abdominal pain, flatulence, and rash. NFV causes a secretory diarrhea through a calcium-dependent process [7]; in adults, administration of calcium carbonate at the same time as NFV may reduce the diarrhea [8] without decreasing plasma concentrations of NFV or its major metabolite, M8 [9]. As with other PIs, new onset diabetes mellitus and exacerbations of previous hyperglycemia have been reported, as has the occurrence of the lipodystrophy syndrome. In a long-term pediatric cohort study of 39 patients receiving NFV as part of HAART, clinically evident lipodystrophy was seen in 11 (28%) children after a median of 49 months [1].

In September 2007, the Department of Health and Human Services issued warnings concerning the presence in NFV of a harmful substance known as ethyl methane sulfonate (EMS), a byproduct of the manufacturing process. EMS is known to be an animal carcinogen, mutagen, and teratogen. For
Pediatric patients who are currently receiving NFV-containing regimens and are stable, the risk-benefit ratio remains favorable for the continued use of NFV. Pediatric patients who need to begin antiretroviral therapy should not be offered regimens containing NFV until further notice, but rather begin an alternative antiretroviral regimen. This is anticipated to be a temporary problem.

**Pediatric Experience**

NFV has been extensively studied in HIV-infected children in combination with other antiretroviral drugs [1, 5, 10-30]. In children between 2–13 years of age receiving NFV as part of triple antiretroviral therapy in randomized trials, the proportion of patients with HIV RNA <400 copies/mL through 48 weeks of therapy has been quite variable, ranging from 26%–69%. Virologic and immunologic response to NFV-based therapy has varied by prior antiretroviral treatment, the number of drugs included in the combination regimen, patient age, and dose used in the study. Highly variable drug exposure remains a significant problem with the use of NFV in pediatric patients. Unpredictable drug exposure may be exacerbated in pediatric patients because of increased clearance compared to adults and difficulties with adherence to adequate food intake with dosing. In earlier studies, lower doses were used (20–30 mg/kg body weight per dose 3 times daily) than are currently recommended (45–55 mg/kg body weight per dose twice daily), accounting for some of the lower response rates. The relatively poor ability of NFV to control plasma viremia in infants and children may be related in part to its reduced potency compared to other PIs or NNRTIs, as shown by studies in adults and adolescents [17, 31]. However, a significant portion of the poor outcome with NFV in children may be related to issues related to palatability of the powder formulation and pharmacokinetic differences in infants, children, and adolescents compared to adults [18]. The pediatric formulation of NFV is a powder that alters the consistency of food or formula to which it is added making the drug unpalatable to some children, who may prefer the bitterness of the crushed tablets to the sandy consistency of food or formula containing NFV pediatric powder. In the PENTA-7 trial, 7 of 20 (35%) infants who started therapy with the NFV powder were switched to crushed tablets because of the difficulty of administering the powder to infants [15].

Better control of plasma viremia has been observed in antiretroviral-naïve than -experienced children receiving NFV. In 2 small studies including 44 antiretroviral-naïve children who received NFV in combination with 2 NRTI drugs, HIV RNA concentrations after 48 weeks of therapy were <400–500 copies/mL in 56%–69% (<50 copies/mL in 44%–48%) of children [11, 12]. In contrast in PACTG 377, a study of antiretroviral-experienced children, response rates (i.e., HIV RNA concentrations <400 copies/mL) to 2 NFV-containing triple therapy regimens (NFV plus stavudine [d4T]/lamivudine [3TC] or d4T/nevirapine [NVP]) in 94 children ranged between 30%–42% after 48 weeks of therapy [14]. Better response rates have been seen with 4-drug regimens in treatment-experienced patients. In 2 studies including 99 children who received NFV combined with 2 NRTIs plus an NNRTI, virologic response with HIV RNA <400 copies/mL after 48 weeks of therapy was observed in 72% of children receiving efavirenz (EFV) and 52% receiving NVP as the NNRTI [13, 14]. In addition, other PIs may be preferable in treatment-experienced patients. When lopinavir/ritonavir (LPV/RTV) was compared to NFV for salvage therapy in 35 treatment-experienced patients after 18 months, 50% of children receiving LPV/RTV had HIV RNA concentrations <400 copies/mL, compared to <20% of children receiving NFV [28].

Antiviral response in children <2 years of age is less than in older children. Agouron study 556 was a placebo-controlled trial of NFV in combination with zidovudine (ZDV)/didanosine (ddI) in 141 minimally pretreated HIV-infected children [32]. For the 94 children ages 2–12 years of age, week 48 HIV RNA concentrations were <400 copies/mL in 26%, compared to 2% of the 47 children <2 years of age. In a study of combination NFV-based therapy in 20 infants with median age of 2.5 months at time of therapy initiation, after 48 and 72 weeks of therapy HIV RNA was <400 copies/mL in 37% and 44%, respectively, and <50 copies/mL in 21% and 25%, respectively [12]. Of 39 PI-naïve children receiving NFV in combination with d4T and 3TC, children with virologic failure at 48 weeks were younger at baseline than responders (0.8 vs. 5.3 years) [11]. Improved virologic response may be seen with NFV-based therapy when it is used as part of a 4-drug regimen in children <2 years of age. In PACTG 356, children <2 years of age were treated with ZDV/3TC/NVP, ZDV/3TC/NVP/abacavir (ABC), or
Studies in adults and children have demonstrated an increased risk of virologic failure associated with low NFV drug exposure, particularly with a NFV C_{min} <1.0 mcg/mL [35-37]. In a study of 32 children treated with NFV 90 mg/kg/day divided into 2 or 3 doses a day, 80% of those with morning trough NFV plasma concentration >0.8 mcg/mL had week 48 HIV RNA concentrations <50 copies/mL, compared to only 29% of those with morning trough <0.8 mcg/mL [38]. It is of note that the median age of the group with C_{trough} <0.8 mcg/mL was 3.8 years, while the median age of the group with C_{trough} >0.8 mcg/mL was 8.3 years [38]. Therapeutic drug monitoring of NFV plasma concentrations, with appropriate adjustments for low drug exposure, results in improved outcome in adults treated with NFV [35, 39]. Given the higher variability of NFV plasma concentrations in infants and children, the benefits of therapeutic drug monitoring and appropriate dose adjustment might be even greater for children. A response rate of 78% was found in a recent pediatric study in which concentrations of NFV and M8 were reported to treating physicians, suggesting a benefit of pharmacokinetic monitoring in children [34]. In PACTG 382, among 50 children ages 3–16 receiving both EFV and NFV, better virologic outcomes (HIV RNA <400 copies/mL) occurred in those patients when NFV AUC_{ss} was greater than the first quartile (>10 mg*h/L) when compared to those below the first quartile: 89% vs. 42%, respectively [30]. Better virologic responses were obtained when doses were adjusted to achieve target AUC values; an approach that requires therapeutic drug monitoring.

References:


Ritonavir (RTV, Norvir®)


See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview

Ritonavir (RTV) is approved for use in children in combination with other antiretroviral agents and is available as liquid and capsule formulations [1]. It has specific activity for HIV-1 and, to a lesser extent, HIV-2. RTV is a potent inhibitor of the cytochrome P450 enzyme pathway and significantly interferes with the metabolism of many medications, including macrolides, fluticasone, and certain antihistamines (see Matrices 2–4 in Appendix A and the product label). Concomitant use of RTV and fluticasone has...
resulted in increased fluticasone concentrations causing decreased serum cortisol concentrations and Cushing syndrome [2-4]. Although RTV inhibits cytochrome P450 CYP3A, it induces its own metabolism. It is well absorbed, with a half-life of 2 to 4 hours in children [5, 6]. Pharmacokinetic studies in HIV-infected children 2–14 years of age may indicate that while RTV clearance is similar to that seen in adults, variability in clearance is likely to be greater in children than in adults due to age-related changes in drug metabolism. Because RTV auto-induces its own metabolism, when RTV is used as the sole PI in full dose in a regimen, it should be started at a lower dose (250 mg per meter² body surface area twice daily) and increased at 2 to 3 day intervals (by 50 mg per meter² body surface area twice daily) to the recommended maximum dose of 350–400 mg per meter² body surface area.

**Resistance**

The most significant genotypic resistance mutations associated with RTV are those found at protease codons 46, 82, 84, and 71. Multiple genotypic mutations are required for resistance to develop, although the 82 mutation appears to be necessary but not sufficient to confer phenotypic resistance. There is cross-resistance between RTV and indinavir (IDV), and many isolates resistant to IDV may also be resistant to saquinavir. Use of one of these agents following the failure of another is not routinely recommended unless viral resistance status is known for the specific PI.

**Adverse Effects**

One small phase I study in children demonstrated a high rate of gastrointestinal intolerance with use of RTV [5]. However, larger studies have shown better tolerance of the drug, particularly when dose escalation is used when initiating therapy. In PACTG 338, approximately 80% of children were able to tolerate RTV at 24 weeks of therapy [7]. Circumoral paresthesia and taste perversion have been reported in adults receiving the drug. Hepatic transaminase elevations exceeding 5 times the upper limit of normal, clinical hepatitis, and jaundice have been reported in adults receiving RTV alone or in combination with other antiretroviral drugs. There may be an increased risk for transaminase elevation in patients with hepatitis B or C virus infection. Caution should be exercised when administering RTV to patients with pre-existing liver disease. Hyperlipidemia is associated with PI use in adults and children and RTV use has been independently associated with increased risk for hypertriglyceridemia in children [8-10].

**Pediatric Experience**

RTV has been studied in HIV-infected children as monotherapy and in combination with other antiretroviral drugs [5-7, 11-19]. Data from several pediatric studies demonstrate that RTV appears safe and is associated with clinical and virologic response in children.

RTV was studied in combination with 1 or 2 NRTIs in children in PACTG 338; there was a mean decrease of >1.5 log in HIV RNA concentrations after 12 weeks of therapy [15]. After 48 weeks of RTV plus 2 NRTIs, 42% of children maintained HIV RNA concentrations below the limit of detection of the assay, compared with 27% of children receiving RTV plus only 1 NRTI. Another small study of PI-naïve children receiving RTV with 2 NRTIs showed an increase of >400 CD4 cells/mm³ after 12 months of therapy [16]. PACTG Protocol 377 randomized antiretroviral experienced, PI- and NNRTI-naïve children to 4 different treatment regimens, including RTV/stavudine (d4T)/nevirapine (NVP). The median increase in CD4 cell count for those on this regimen was 254 cells/mm³, and 41% of children had HIV RNA <400 copies/mL at 24 weeks of treatment [17].

As in adults, RTV can be used as a pharmacokinetic enhancer of other PIs in children. RTV acts by inhibiting the metabolism of the other PI, therefore increasing the plasma concentration of the second PI. Lopinavir/RTV, a PI coformulation, has been well studied in children and is the preferred PI for initial therapy in children (see Lopinavir/Ritonavir). However, while other RTV-boosted PI regimens are promising and dosing has been well studied in adults, the appropriate dosing in children and adolescents is not known for the different possible PI combinations. For example, small studies have evaluated use of low-dose RTV to increase concentrations of IDV in an every 12-hour dosing regimen in children [18-21]. Additional pharmacokinetic studies are necessary before more definitive dosing recommendations can be made.

Similar to other PIs, clearance of RTV is greater in young infants than in older children and adults. Preliminary data from PACTG 345, which evaluated RTV alone and in combination with lamivudine and zidovudine in children <2 years of age, demonstrated that concentrations are highly variable, and doses of...
350–450 mg/m² twice a day may not be sufficient for long-term suppression of viral replication in this age group [11].

Although RTV has been well studied, its use in children as a sole PI for initial therapy is recommended only under certain circumstances. RTV is associated with a higher incidence of gastrointestinal toxicity and has a greater potential for drug-drug interactions than other PIs. Poor palatability of the liquid preparation and large pill burden with the capsules (adult dose is 6 capsules twice daily) limit its use as a sole PI. Most RTV use in adults and children is as a pharmacokinetic enhancer with other PIs.

References:


### Saquinavir (SQV, Invirase®)


**See Also:** Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**

In 1995, saquinavir (SQV) became the first PI approved for use in adults and adolescents >16 years of age in combination therapy with NRTIs. In its original formulation as a hard gel capsule (Invirase), it had very limited bioavailability (~ 4%) following oral administration. In 1997, the FDA approved a soft gel capsule preparation (Fortovase) with significantly enhanced oral bioavailability. In 2003, the FDA approved Invirase for use in boosted dosing regimens with ritonavir (RTV), allowing for twice daily dosing. In February 2006, the sale and distribution of Fortovase was discontinued and replaced by the 200 mg capsule and 500 mg film coated tablet formulations of Invirase. SQV has not been formally approved for use in children, and is not yet available in a liquid preparation.

SQV is more than 90% metabolized by cytochrome P450 3A4 isoenzymes, the same enzyme system which metabolizes RTV. RTV, nelfinavir (NFV), and lopinavir (LPV)/RTV have been shown to inhibit the metabolism of SQV; plasma concentrations of SQV are increased when it is coadministered with these agents. As with the other PIs, multiple pharmacological interactions are possible with coadministered agents that are also metabolized by CYP3A4. A study of omeprazole, a proton-pump-inhibitor, with RTV boosted SQV in healthy adults showed an increase of 82% in saquinavir exposure.

Because of low bioavailability SQV should only be used in adults when administered with another PI. Such “SQV boosting” has been studied in adults using NFV, RTV, LPV/RTV, or atazanavir (ATV) as the second PI [2-10]. Several studies in adults have examined once daily regimens of SQV (1200–1600 mg) boosted by RTV/ATV or RTV [11-13].

**Resistance**

Resistance to SQV is associated with a unique mutation pattern in the HIV protease gene, primarily in codons coding for amino acids at positions 48 and 90. Secondary mutations, which also contribute to resistance, may occur at amino acid positions 10, 54, 71, 73, 77, 82, and 84. Viral isolates resistant to SQV are not necessarily resistant to the other PIs. However, phenotypic resistance to NFV has been demonstrated following SQV use, despite the lack of the usual NFV resistance mutations (e.g., D30N), perhaps caused by the secondary resistance mutations selected for by SQV, especially at positions 54 and 82 [14]. Continued use of SQV without complete virologic suppression may lead to cross-resistance with other PIs due to the accumulation of secondary mutations. Viral isolates resistant to RTV and indinavir are usually also resistant to SQV.

**Adverse Effects**

The drug is usually well tolerated; mild gastrointestinal disturbances (e.g., diarrhea, nausea, abdominal pain) and reversible elevations in liver function tests are the most common side effects reported in adults. As with all agents in this class, new onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, hyperglycemia, and diabetic ketoacidosis have been reported with the use...
of SQV. Elevated cholesterol and triglyceride concentrations have been reported in some children taking SQV in combination with RTV [15].

Pediatric Experience
SQV has been studied in HIV-infected children with NRTIs and other PIs [2, 16-20]. Initial studies in children demonstrated that the pharmacokinetics of the soft gel formulation of SQV were different than that in adults; SQV administered as the sole PI resulted in concentrations much lower than observed in adults, and did not reliably provide effective plasma drug concentrations in children [16, 17]. In one study, children <24 kg receiving a 50 mg/kg/dose every 8 hours had drug exposures similar to that in adults. However, children >28 kg required approximately 2-fold higher doses than the adult dose (1200 mg every 8 hours) to gain more acceptable SQV drug exposure [18]. Thus, combination of SQV with another PI that would increase drug exposure will also be required in children, but data on the appropriate drug doses for children are not yet available.

SQV in combination with NFV, RTV, or LPV/RTV has been studied in pediatric patients [2, 16-19]. Administration of SQV in combination with NFV (33 mg/kg SQV and 30 mg/kg NFV, both given 3 times daily) resulted in increased SQV exposure in children to concentrations that approached those observed in adults [18]. In 13 children receiving this regimen, the median change in HIV RNA levels was 2.58 log copies/mL, with 62% of children having HIV RNA concentrations <50 copies/mL at 48 weeks [17]. In a study of 23 pediatric patients, a significant correlation between average trough concentration and sustained viral suppression was observed, with an apparent threshold mean trough SQV concentration >200 ng/mL correlating with sustained viral suppression [18].

While both SQV/RTV and SQV/LPV/RTV regimens are promising, the appropriate dosing in children and adolescents for the different possible PI combinations is not known. Additional pharmacokinetic studies are necessary before more definitive dosing recommendations can be made.

References:


**Tipranavir (TPV, Aptivus®)**


See Also: [Appendix A: Characteristics of Available Antiretroviral Drugs](#)

**Overview**

Tipranavir (TPV) is a non-peptidic HIV-1 protease inhibitor. TPV coadministered with ritonavir (RTV)
was approved by the FDA in June 2005 for treatment of HIV-1 infection in adult patients who are highly treatment experienced or have HIV-1 strains resistant to multiple PIs, and who have evidence of viral replication. The indication and approval of TPV/RTV was based on analyses of HIV RNA concentrations documented in 2 controlled studies (RESIST-1 and RESIST-2) of TPV/RTV given over 24 weeks to adults with clinically advanced disease and treatment experience with 3 classes (NRTI, NNRTI, and PI) of antiretroviral drugs [1, 2]. Only limited data are available on TPV/RTV in HIV-infected children.

TPV must be coadministered with RTV to exert its therapeutic effect. TPV and RTV are not coformulated and must be given twice daily as the 2 separate products. Failure to correctly coadminister TPV with RTV will result in plasma concentrations of TPV that are insufficient to achieve the desired antiviral effect and will alter some of the known drug-drug interactions.

Several clinically important points were identified in the review of the pivotal trials. The use of other active agents with TPV/RTV was associated with a greater likelihood of treatment response. Genotypic or phenotypic testing and treatment history should guide the use of TPV/RTV because the number of baseline primary PI mutations affects the virologic response (see below under “Resistance”).

Metabolism of TPV is complex. TPV is a CYP3A substrate, an inhibitor of multiple other cytochrome P450 enzymes, and a P-glycoprotein (P-gp) substrate and apparent inducer. When combined with RTV, the net effect is CYP3A inhibition and P-gp induction. The extensive drug-drug interaction potential of TPV/RTV when coadministered with multiple classes of drugs must be considered prior to and during use of TPV/RTV.

Resistance
Analyses of HIV-1 genotypes in heavily treatment-experienced adults demonstrated that mutations at 16 amino acid codons of the protease gene were associated with reduced susceptibility to TPV: L10V, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, 154A/M/V, Q58E, H69K, T74P, V82L/T, N85D, and 184V. In the pivotal trials (RESIST-1 and RESIST-2), response to TPV/RTV decreased with increasing numbers of protease mutations. Response rates were reduced if ≥5 PI-associated mutations were present at baseline and if subjects did not receive concomitant enfuvirtide. TPV/RTV was associated with better virologic responses in patients with similar numbers of baseline PI mutations than the responses to the comparator PI/RTV [3].

Adverse Effects
In adult patients, the most commonly reported adverse effects observed with the use of TPV/RTV included diarrhea, nausea, fatigue, headache, and vomiting. Mild to moderate rashes have been reported in subjects receiving TPV/RTV, and were reported in more female than male patients. In one drug interaction study of TPV/RTV with oral ethinyl estradiol, 33% of healthy female volunteers developed rash. TPV contains a sulfa moiety and should be used with caution in patients with known sulfonamide allergy.

Treatment with TPV/RTV has been associated with large increases in total cholesterol and triglycerides. Cholesterol and triglyceride testing should be performed prior to initiating TPV/RTV and at periodic intervals during therapy.

TPV/RTV has been associated with reports of clinical hepatitis and hepatic decompensation, including some fatalities. For all patients, liver function tests should be performed at initiation of treatment with TPV/RTV and monitored frequently throughout treatment. Patients with chronic hepatitis B or hepatitis C coinfected are at increased risk for developing worsening transaminase elevations or hepatic decompensation and warrant extra vigilance. TPV is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B and C).

TPV, coadministered with 200 mg of RTV, has been associated with reports of both fatal and non-fatal intracranial hemorrhage in HIV-infected adults. Many of these patients had other medical conditions or were receiving concomitant medications that may have caused or contributed to these events. No pattern of abnormal coagulation parameters has been observed in patients in general, or preceding the development of intracranial hemorrhage. Therefore, routine measurement of coagulation parameters is not currently indicated in the management of patients on TPV [1]. TPV should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery or other medical conditions, or who are receiving medications known to increase the
risk of bleeding such as antiplatelet agents and anticoagulants, or who are taking supplemental high doses of vitamin E. (http://www.fda.gov/medwatch/SAFETY/2007/May_PI/Aptivus_PI.pdf)

Pediatric Experience
There are only limited data on the safety, efficacy, and pharmacokinetics of TPV/RTV in pediatric patients. An oral liquid formulation is under investigation in PACTG 1051/BI1182.14.

TPV pharmacokinetics of the liquid formulation at steady state were assessed in 52 children in 3 age groups (1 antiretroviral-naïve child, 51 antiretroviral-experienced children): 2–6, 6–12, and 12–18 years [4]. TPV/RTV oral solutions were administered at doses of 290/115 and 375/150 mg/meter² body surface area twice daily in combination with standard of care background medication. TPV trough concentrations for pediatric patients receiving TPV/RTV 290/115 mg/meter² body surface area were consistent with TPV trough concentrations achieved in adults receiving standard TPV/RTV 500 mg/200 mg dosing. The higher dose (375/150 mg/meter² body surface area) reflected a 30% increase in the adult dose. Population pharmacokinetic analysis demonstrated that TPV clearance can be affected by body weight and that volume of distribution can be affected by age.

Virologic and immunologic data from 48 weeks of therapy in 115 children (all but 3 treatment-experienced) enrolled in the above trial were analyzed [5, 6]. Among patients receiving the lower dose (TPV/RTV 290/115 mg/meter² body surface area), 40% achieved HIV RNA <400 copies/mL and 35% <50 copies/mL after 48 weeks; among those receiving the higher dose (TPV/RTV 375/150 mg/meter² body surface area), 46% achieved HIV RNA <400 copies/mL and 35% <50 copies/mL after 48 weeks of therapy. TPV treatment was associated with a mean increase in CD4 cell count of 157 cells/mm³ and 96 cells/mm³ in lower and higher dose groups, respectively. TPV/RTV was well-tolerated; 4% of children experienced a drug-related serious adverse event, and 9% of patients discontinued study drugs due to adverse events. The most common adverse events were gastrointestinal disturbances. Moderate or severe laboratory toxicity was seen in 11% of children (primarily increase in GGT and CPK). Virologic outcome was predicted by genotypic inhibitory quotient (GIQ), a measure of the median TPV trough concentration divided by the number of TPV mutations. The GIQ was consistently greater in the high dose, TPV/RTV 375/150 mg/meter² body surface area /6/. Based on these findings, the high dose regimen has been recommended for all study participants.

References:
Entry and Fusion Inhibitors

Enfuvirtide (Fuzeon™, T-20)


See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

Overview

Enfuvirtide (T-20) was approved in March 2003 for HIV-infected adults and children >6 years of age for use in combination with other antiretroviral drugs for the treatment of HIV infection in treatment experienced patients with evidence of HIV replication despite ongoing antiretroviral therapy. T-20 is a novel, synthetic, 36 amino acid peptide that binds to a region of the HIV envelope glycoprotein gp41; this binding prevents fusion of the virus envelope with the membrane of the CD4 host cell. It is a potent and selective inhibitor of HIV-1 entry in vitro, and has induced virologic responses in phase III clinical trials in adults and in phase I/II trials in children [1-6]. In trials of novel agents such as integrase inhibitors or newer PIs, individuals who were naïve to T-20 and added it to their optimized background regimen had superior results when compared to those with prior T-20 experience [7, 8].

T-20 comes as a sterile powder that must be reconstituted with sterile water and administered by subcutaneous injection. Each injection should be given at a site different from the preceding injection site, and should not be injected into moles, scar tissue, bruises, or the navel. T-20 is approximately 92% protein bound, predominantly to albumin. As a peptide, T-20 undergoes catabolism to its constituent amino acids, with subsequent recycling of the amino acids into the general body pool. T-20 does not affect the metabolism of drugs metabolized by liver CYP450 enzymes.

Resistance

Clinical isolates of HIV that are resistant to NRTIs, NNRTIs, and PIs remain susceptible to T-20 in cell culture. However, HIV isolates with reduced susceptibility to T-20 have been selected in vitro, although primary resistance to T-20 in patients without prior T-20 treatment is very rare [9]. The results from in vitro studies indicate that two amino acid substitutions (G36S and V38M) within the HR1 region of the HIV gp41 glycoprotein can lead to T-20 resistance [10]. In clinical trials in adults, HIV isolates with reduced susceptibility to T-20 have been recovered, demonstrating that HIV quasispecies in infected patients can undergo in vivo selection of resistant variants as a result of T-20 therapy. Decreases in susceptibility ranging from 4- to 422-fold relative to baseline virus have been observed with genotypic changes in gp41 amino acids 36 to 45 and that this can occur within 2 weeks of initiating a T-20, non-suppressive regimen [11]. A recent report suggests that there is a relationship between V38 mutants and persistent increases in CD4 counts while Q40 mutants appear to have persistent loss of CD4 cells [12]. Antibodies to HIV-1 gp41 that are cross-reactive to T-20 do not appear to decrease its clinical efficacy [13].

Adverse Effects

Local injection site reactions are common, occurring in 98% of adults and 87% of children, although only a few patients report this as the sole reason for T-20 discontinuation. Symptoms included pain and discomfort, induration, erythema, nodules and cysts, pruritis, and ecchymosis. Although infection is uncommon (1% of patients), caregivers should monitor injection sites carefully for signs or symptoms of cellulitis or local infection. Biopsies of local cutaneous reactions indicated a variety of pathologies, including a chronic scleroderma-like pathology, suggesting that injection sites should be rotated [14]. There are reports in adults of fewer and less severe injector site reactions if alternative delivery systems (e.g., Biojector) are used when contrasted to routine injections [15]. An increased rate of bacterial pneumonia (4.7 pneumonia events per 100 patient-years) was observed in T-20 – treated adults in phase III studies compared to the control arm – the relation of this finding to T-20 use is uncertain. However, patients should be monitored for signs and symptoms of pneumonia, particularly if they have a low initial CD4 cell count, high initial viral load, history of prior lung disease, or are intravenous drug users or smokers (a particular concern in adolescents). Other adverse events reported in trials include insomnia, myalgia, peripheral neuropathy, and depression.

Serious hypersensitivity reactions are rare. Symptoms include rash, fever, nausea and vomiting, chills, hypotension, and elevated liver transaminases; other presumably immune-mediated symptoms include respiratory distress, glomerulonephritis with hematuria, and Guillain-Barre syndrome. If such symptoms occur, therapy with T-20 should be...
discontinued and should not be restarted, as hypersensitivity may recur on rechallenge. Treatment-related eosinophilia occurred in 11.2% of adults in a phase III trial, compared to only 2.4% of control patients [14]. However, eosinophilia was not associated with clinical events suggestive of systemic hypersensitivity.

In the pediatric trials of chronic T-20 use, no life-threatening adverse events attributable to T-20 were identified, and no systemic serious toxicities were related to T-20 administration. Commonly encountered findings included wheezing episodes, respiratory infections, nausea, vomiting and other typical pediatric maladies and, in general, were judged not to be related to T-20 use. In one study, 2 children died; 1 with preexisting pneumonitis prior to T-20 initiation who died as a result of multiorgan failure and mitochondrial toxicity, and the second succumbed to septicemia [6]. As in adult trials, injection site reactions were frequent and have been observed in 79%-87% of children in pediatric studies; they usually begin shortly after treatment initiation and are mild although, in one study, 7% of children experienced cellulitis [4, 6]. Grade III and IV laboratory anomalies were infrequently observed and were not judged to be related to T-20 experience.

**Pediatric Experience**

T-20 has been studied in HIV-infected children in combination with other antiretroviral drugs [4-6, 16, 17]. PACTG 1005 initially studied T-20 in 14 HIV-infected children aged 4–12 years with incomplete viral suppression on their current antiretroviral regimen (plasma HIV RNA concentrations >10,000 copies/mL while receiving a stable combination of 2 NRTIs plus an NNRTI or a PI for ≥16 weeks) [4]. Part A included a single-dose pharmacokinetic evaluation of T-20 given subcutaneously and then intravenously at 15, 30, or 60 mg per meter² of body surface area. The dose of T-20 that reliably resulted in the target trough concentration (1,000 ng/mL) was 60 mg per meter² of body surface area per dose, the approximate “equivalent” of a 90 mg dose delivered to a typical adult with a body surface area of 1.7 meter². This resulted in the recommended pediatric label dose in children aged 6–16 years of 2 mg/kg (maximum 90 mg) twice daily administered subcutaneously. In a second pediatric study of 25 children aged 5–16 years, the 2 mg/kg dose, with a maximum dose of 90 mg was found to yield drug concentrations similar to 60 mg per meter² of body surface area dose and that drug exposure was independent of age group, body weight, body surface area, and surface maturation [18]. Further data are needed in children <6 years of age. No metabolic induction or inhibition of T-20 was observed in PACTG 1005, nor was there a statistical relationship, within the utilized dosing schedule, between drug exposure with this agent and virologic benefit [16].

Part B of PACTG 1005 evaluated the safety and antiretroviral activity of chronic twice daily subcutaneous T-20 administration at 60 mg per meter² of body surface area per dose. For 7 days, the drug was added to each child’s background antiretroviral regimen; at day 7, each child’s background therapy was changed to a regimen that was predicted to be virologically active, while T-20 was continued. Children were followed for up to 96 weeks on the study. Two elected to discontinue T-20 within 24 weeks (1 due to injection aversion, 1 due to a surgical procedure), 4 discontinued due to virologic failure (defined as >1 log increase in viral load above baseline), and 2 discontinued due to Grade 3 toxicity. In this cohort, most children had local injection site reactions. 79% of children had >0.7 log reduction in HIV RNA by day 7. At 24 weeks of treatment, 71% had a >1.0 log reduction, 43% were suppressed to <400 copies/mL, and 21% were suppressed to <50 copies/mL [5]. However, only 36% of children maintained virologic suppression (>1.0 log decrease in HIV RNA) at week 96 [17]. Significant improvements in CD4 percentage and height z-score were observed in children receiving T-20 for 48 and 96 weeks.

T20-310, a phase I/II study of T-20 (2.0 mg/kg subcutaneously, maximum 90 mg, twice daily) plus an optimized background antiretroviral regimen enrolled 52 treatment experienced children, 3–16 years of age for 48 weeks. Of those completing 48 weeks of therapy (64%), the median decrease in HIV RNA was -1.17log10 copies/mL (n=32) and there was a median increase of 106 cells/mm³ (n=25).

Treatment responses at week 8 were superior in children when contrasted with adolescents as measured by plasma HIV RNA change from baseline (-2.85 vs. -0.12 log10 copies/mL) or those maintaining HIV RNA <400 (42% vs. 4%). Median increases in CD4 count were 257 cells/mm³ in children and 84 cells/mm³ in adolescents. The observed differential responses between children and adolescents probably reflects unique challenges to adherence with the prescribed regimen [6].

**Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection**

February 28, 2008
References:


Maraviroc (MVC, Selzentry®)

See Also: Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**
Maraviroc (MVC) is a CCR5 coreceptor antagonist indicated for combination antiretroviral treatment of adults infected HIV-1 that is solely CCR5-tropic, and who have evidence of viral replication and HIV-1
strains resistant to multiple antiretroviral agents. MVC was approved by the FDA in August 2007 based on analyses of HIV RNA concentrations documented in two controlled studies of MVC given over 24 weeks to clinically advanced 3-class antiretroviral (NRTI, NNRTI, PI, or enfuvirtide) treatment-experienced adults with evidence of HIV replication despite ongoing antiretroviral therapy. There are no study results demonstrating the effect of MVC on clinical progression of HIV infection in adults, and there are no data available on MVC in HIV-infected children or adolescents <16 years of age [1, 2].

Tropism testing and treatment history should guide the use of MVC. Use of MVC is not recommended in patients with testing that reveals the presence of HIV with dual/mixed CXCR4/CCR5 tropism, or pure CXCR4 tropism as a lack of efficacy was demonstrated in phase II studies in patients in this category.

MVC is a substrate of cytochrome P450 enzymes (principally CYP3A4), a P-glycoprotein (P-gp), and its clearance is substantially influenced by inhibitors and inducers of these enzymes. The extensive drug-drug interaction potential of MVC when coadministered with multiple classes of drugs must be considered prior to and during its use.

Resistance

MVC selectively binds to the human chemokine receptor CCR5 present on the cell membrane, preventing the interaction of HIV gp120 and CCR5 which is necessary for CCR5-tropic virus to enter CD4 cells. The entry of CXCR4-tropic and dual-tropic HIV into CD4 cells is not inhibited by MVC, and drug resistant variants can be selected in vitro. In pivotal clinical trials, CXCR4-using (i.e., CXCR4- or dual/mixed-tropic) virus was detected in patients at the time of failure which was not detected by the tropism assay prior to treatment. A detailed clonal analysis revealed that CXCR4-using virus in these subjects emerged from a low concentration of pre-existing CXCR4-using virus that was not detected by the tropism assay (which is population-based) prior to treatment rather than from a coreceptor switch from CCR5-tropic virus to CXCR4-using virus resulting from mutation in the virus. The resistance profile of MVC is complex, and experience with genotypic resistance assays is too limited at present to endorse their use [3-5].

Adverse Effects

In adults with twice daily MVC therapy, the most common adverse events reported were cough, fever, upper respiratory tract infections, rash, musculoskeletal symptoms, abdominal pain, and dizziness. Additional adverse events that occurred with once daily dosing at a higher rate than both placebo and twice daily dosing were diarrhea, edema, influenza, esophageal candidiasis, sleep disorders, rhinitis, parosomnias, and urinary abnormalities. Most of the adverse events reported were judged to be mild to moderate in severity. Cardiovascular events, including myocardial ischemia or infarction, have been observed at higher rates in MVC-treated patients than in placebo. QT prolongation has been observed in animal studies at up to 12 times the recommended human dosage, but no prolongation has been noted in treatment-experienced patients taking recommended dosages. When given to HIV-infected patients in phase III studies at recommended dosages, no greater rates of postural hypotension were observed. However, the dose-limiting adverse effect in clinical studies, observed at daily doses of MVC 600 mg, is postural hypotension.

Hepatotoxicity has been reported with MVC use. Evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE) prior to the development of hepatotoxicity may occur. Patients with signs or symptoms of hepatitis or allergic reaction following use of MVC should be evaluated immediately. The safety and efficacy of MVC have not been specifically studied in patients with significant underlying liver disorders, and only a small number of subjects who were coinfected with hepatitis B or hepatitis C participated in pivotal trials. Caution should be used when administering MVC to patients with pre-existing liver dysfunction or who are coinfected with hepatitis B or C viruses.

Pediatric Experience

The pharmacokinetics, safety, and efficacy of MVC in patients <16 years of age have not been established. The manufacturer has made post-marketing commitments to studies of MVC in infants and children, and clinical trials are currently being designed.

References:


Page 62

Supplement I: Pediatric Antiretroviral Drug Information
INTEGRASE INHIBITORS

**Raltegravir (RAL, Isentress®)**


*See Also:* Appendix A: Characteristics of Available Antiretroviral Drugs

**Overview**

Raltegravir is an integrase inhibitor indicated for combination antiretroviral treatment of treatment-experienced adult patients who have evidence of viral replication and HIV-1 strains resistant to multiple antiretroviral regimens. Raltegravir interferes with the strand transfer activity of the HIV integrase protein, which inserts the viral DNA into the host cell chromosome to form the viral provirus. Raltegravir was approved by the FDA in October 2007 based on safety and efficacy data from two 24 week long studies involving treatment experienced adult patients with documented resistance to ≥1 drug in each of 3 classes (NRTI, NNRTIs, PIs) [1].

Raltegravir is also being studied in treatment-naïve patients [2]. In one study, viral loads became undetectable more rapidly in patients who received raltegravir at any dose than in those who received efavirenz. However, the antiretroviral activity of raltegravir was otherwise similar to efavirenz after 24 and 48 weeks of therapy.

The major mechanism of clearance of raltegravir in humans is UGT1A1-mediated glucuronidation. Raltegravir should be used with caution when administered with strong inducers of UGT1A1, including rifampin, which may reduce plasma concentrations of raltegravir.

In adults, the pharmacokinetics of raltegravir are substantially altered by food. A high fat meal delays the absorption of the drug, and leads to a marked increase in drug exposure. However, raltegravir was dosed with or without food in phase II and phase III trials, without marked differences in adverse effects. Consequently, raltegravir can be taken with or without food.

**Resistance**

Resistance to raltegravir is associated with integrase mutations at either Q148 or N155. Additional mutations are commonly seen, which further enhance resistance.

**Adverse Effects**

The most common adverse reactions (>10%) of all intensities, reported in subjects in either raltegravir or the placebo treatment group, regardless of causality were: nausea, headache, diarrhea, and fever.

Creatine kinase elevations have been observed in subjects who received raltegravir. Myopathy and rhabdomyolysis have been reported but the relationship of raltegravir to these events is not known. The drug should be used with caution in patients at increased risk of myopathy or rhabdomyolysis, such as patients receiving concomitant medications known to cause these conditions.

**Pediatric Experience**

The pharmacokinetics, safety and efficacy of raltegravir in patients <16 years of age have not been established. Studies involving children and adolescents are underway, and the manufacturer has made a commitment to studying the pharmacokinetics in HIV-infected infants as young as 4 weeks of age.

**References:**
