REVIEW ARTICLE

New Antiretroviral Therapies for Pediatric HIV Infection

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Human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome affect millions of children worldwide. The development of antiretroviral therapy has significantly improved the morbidity and mortality of pediatric patients infected with HIV. Currently, 4 classes of antiretroviral agents exist: nucleoside / nucleotide reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, and entry inhibitors. A total of 21 single-entity antiretroviral agents and 4 co-formulated antiretroviral products hold Food and Drug Administration (FDA) approval for treatment of HIV-1 infection. However, not all of these agents are indicated for use in patients less than 18 years of age. Since the year 2000, 7 new antiretroviral agents (atazanavir, emtricitabine, enfuvirtide, fosamprenavir, lopinavir/ritonavir, tenofovir, and tipranavir) have been approved by the FDA for use in adult patients as part of combination therapy for the treatment of HIV-1 infection. Although only 3 of these newer agents (emtricitabine, enfuvirtide, and lopinavir/ritonavir) are currently FDA approved for use in pediatric patients, pediatric clinical studies of the other 4 new agents are currently underway. The purpose of this article is to review these 7 new antiretroviral agents and describe their roles in the treatment of pediatric HIV infection. For each drug, the following information will be addressed: FDA-approved indication and age groups, clinical efficacy, pharmacokinetics, adverse drug reactions, clinically relevant drug interactions, pediatric and adult dosing, dosage forms, administration, and place in the treatment of pediatric HIV infection.

KEYWORDS AIDS, amprenavir, antiretroviral agents, emtricitabine, enfuvirtide, fosamprenavir, HIV, lopinavir/ritonavir, tenofovir, tipranavir

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INTRODUCTION

Infection with human immunodeficiency virus (HIV) and the acquired immunodeficiency syndrome (AIDS) inflict significant morbidity and mortality on millions of children worldwide. In 2005, of the 3.1 million deaths attributed to AIDS, 570,000 occurred in children less than 15 years of age.[1] A large population of pediatric patients live with this devastating illness. Currently 2.3 million children less than 15 years of age are infected with HIV.[1] Cumulatively through 2003, nearly 10,000 cases of AIDS in children < 13 years of age have been reported in the United States.[2] These reported numbers may significantly underestimate the actual number of children afflicted by this disease.

The advent of potent antiretroviral therapy has significantly increased the survival of both adults and children infected with HIV.[3] Currently available medications cannot cure HIV infection but can significantly decrease the morbidity and mortality associated with both HIV and AIDS. As the antiretroviral ar-

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senal grows, options for pediatric HIV therapy continue to improve. Four categories of antiretroviral agents are available for treatment of HIV, including nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs/NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and entry inhibitors. Currently, 21 single entity antiretroviral agents are approved by the United States Food and Drug Administration (FDA), along with several co-formulations. The number of agents approved for use in pediatric patients is not quite as extensive (Tables 1-4). In addition to the lack of FDA approval in all age groups, the lack of pediatric dosage forms continues to be an obstacle in the treatment of pediatric HIV infection. Of the 25 commercially available products only 11 are available as an oral solution or powder for suspension (Tables 1-4). Several disadvantages of commercially available oral liquid antiretroviral agents also exist. Poor palatability, volume of medication per dose, large quantity of medication which must be carried home monthly from the pharmacy, and risk of inaccurate dosing are concerns with the current formulations.

ABBREVIATIONS: ABC, abacavir; AIDS, acquired immunodeficiency syndrome; APV, amprenavir; ATV, atazanavir; AUC, area-under the plasma concentration-time curve; BMD, bone mineral density; CYP450, cytochrome P450; d4T, stavudine; ddc, zalcitabine; ddI, didanosine; DLV, delavirdine; EFV, efavirenz; FDA, Food and Drug Administration; FPV, fosamprenavir; FTC, Emtricitabine; H2-blockers, histamine-2 receptor blockers; HDL-C, high density lipoprotein cholesterol; HIV, human immunodeficiency virus; HR, heptad repeat regions; IDV, indinavir; LPV/RTV, lopinavir/ritonavir; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NtRTI, nucleotide reverse transcriptase inhibitor; NVP, nevirapine; P-gp, P-glycoprotein; PI, protease inhibitor; PPI, proton-pump inhibitor; RTV, ritonavir; SQV, saquinavir; TDF, Tenofovir disoproxil fumarate; 3TC, lamivudine; TPV, tipranavir; T-20, enfuvirtide; UTG1A1, uridine diphosphate glucuronosyl 1A1; ZDV, zidovudine

Potent antiretroviral therapy provides significant clinical benefit to HIV-infected pediatric patients with immunologic and clinical symptoms of this disease.[3] Clinical trials have shown substantial improvement in growth and neurodevelopment, as well as in immunologic and virologic status. Initiation of antiretroviral therapy is based on the evaluation of a number of factors. These factors include: severity of disease and risk of disease progression; availability of appropriate drug formulations for children; potency, complexity, and potential adverse effects of the antiretroviral regimen; effect of the regimen on future antiretroviral therapeutic options; presence of co-morbid conditions; potential drug-drug and drug-food interactions; and ability of the caregiver and/or patient to adhere to the regimen. The decision to initiate antiretroviral therapy in a pediatric patient may vary depending on the patient age, clinical category, and immune category. Recommendations for initiating antiretroviral therapy in pediatric patients are listed in Tables 5 and 6.

Once the decision to initiate antiretroviral therapy has been made, the clinician is then faced with the challenge of which combination of agents to choose. As with the decision to initiate therapy, one must consider the short and long-term effects of the initial antiretroviral regimen. Guidelines exist for both adult and pediatric patients to assist the clinician's choice of initial regimen.[3,4] Recommendations for preferred and alternative regimens, as well as regimens that are not recommended for initial use, are available and listed in Tables 7 and 8.[3,4]

This article will focus on the antiretroviral agents that have recently been approved for use in the treatment of HIV-1 infection and the role of these agents in the treatment of pediatric HIV infection. The specific agents which will be discussed include emtricitabine, tenofovir, atazanavir, fosamprenavir, lopinavir/ritonavir, tipranavir, and enfuvirtide. A discussion of all currently available antiretroviral agents as well as guidelines for treating and monitoring HIV infection in pediatric and adolescent patients is beyond the scope of this article. The reader is directed to the "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV-infection" and "Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents" available at http://www.aidsinfo.nih.gov/guidelines.[3,4]

PHARMACOTHERAPY

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs / NtRTIs)

The nucleoside reverse transcriptase in-

Table 1. Currently Available Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)[3]

Abbreviation	Generic Name (Brand Name)	FDA Approved Age	Formulations
NRTIs			
ABC	Abacavir (Ziagen)	≥ 3 mo	Oral Solution: 20 mg/mL Tablet: 300 mg
ddI	Didanosine (Videx)	≥ 2 wk	Powder for Oral Solution: 10 mg/mL
	Didanosine EC (Videx EC)	≥ 18 yr	Delayed-release capsule: 125 mg; 200 mg,* 250 mg,* 400 mg*
FTC	Emtricitabine (Emtriva)	≥ 3 mo	Oral Solution: 10 mg/mL Capsule: 200 mg
3TC	Lamivudine (Epivir)†	≥ 3 mo	Oral Solution: 10 mg/mL Tablets: 150 mg, 300 mg
d4T	Stavudine (Zerit)	Newborn – adult	Oral Solution: 1 mg/mL Capsule: 15 mg, 20 mg, 30 mg, 40 mg
ddC	Zalcitabine (Hivid)	≥ 13 yr	Tablet: 0.375 mg, 0.75 mg
ZDV	Zidovudine (Retrovir)	Newborn – adult	Oral Syrup: 10 mg/mL* Capsule: 100 mg* Tablet: 300 mg* Solution for IV Infusion: 10 mg/mL
NtRTIs			
TDF	Tenofovir (Viread)	≥ 18 yr	Tablet: 300 mg

mo, months; wk, weeks; yr, years
** generic formulation available*
† Lamivudine is also available as Epivir HBV, which is indicated for the treatment of hepatitis B virus.
The commercially available formulations include a 100 mg tablet and a 5 mg/mL oral solution.

hibitors (NRTIs) were the first class of drugs approved for use in the treatment of HIV infection. Both the NRTIs and nucleotide reverse transcriptase inhibitors (NtRTIs) are considered nucleoside analogs since their structures resemble nucleic acids. Intracellular phosphorylation is necessary for activation of these agents.[3] Following intracellular phosphorylation, the NRTIs and NtRTIs competitively inhibit viral reverse transcriptase which prematurely terminates DNA synthesis and inhibits viral replication. Structurally the NRTIs and NtRTIs differ; the NtRTIs already possess one phosphate molecule. This phosphate molecule eliminates the first and often rate-limiting phosphorylation step, thus giving the NtRTIs a potential therapeutic advantage.

Several adverse effects are unique to the NRTIs and NtRTIs. The nucleoside analogs are not specific for HIV DNA and can inhibit mitochondrial DNA polymerase gamma which can lead to mitochondrial dysfunction.[3] Mitochondrial dysfunction may clinically manifest as lactic acidosis, hepatic steatosis, pancreatitis, myopathy, cardiomyopathy, and peripheral neuropathies. The risk of mitochondrial dysfunction is not equal among the nucleoside analogs. Zalcitabine, didanosine, stavudine, and zidovudine are the most likely NRTIs to inhibit DNA polymerase gamma and cause mitochondrial toxicities. While the risk of mitochondrial toxicity appears to be reduced with the NtRTIs, adverse reactions associated with mitochondrial toxicity have been reported.[5]

Currently, 7 single-entity NRTIs and 1 single-entity NtRTI are FDA approved for use in the treatment of HIV infection (Table 1).[3] Not all of these agents have pediatric approval or are available in pediatric dosage forms. Six NRTIs (abacavir, didanosine, emtricitabine, lamivudine, stavudine, and zidovudine) are approved for children < 12 years and are available as oral liquids or powders for reconstitution. One additional NRTI (zalcitabine) is approved

Table 2. Currently Available Antiretroviral Combination Products[3]

Abbreviations	Generic Name (Brand Name)	FDA Approved Age	Formulations
NRTIs			
ABC + 3TC	Abacavir/lamivudine (Epzicom)	≥ 18 yr	Tablet: 600 mg (ABC) + 300 mg (3TC)
ABC + 3TC + ZDV	Abacavir/lamivudine/ zidovudine (Trizivir)	Adolescents ≥ 40 kg – adult	Tablet: 300 mg (ABC) + 150 mg (3TC) + 300 mg (ZDV)
3TC + ZDV	Lamivudine/zidovudine (Combivir)	≥ 12 yr	Tablet: 150 mg (3TC) + 300 mg (ZDV)
NRTIs + NtRTIs			
FTC + TDF	Emtricitabine/tenofovir (Truvada)	≥ 18 yr	Tablet: 200 mg (FTC) + 300 mg (TDF)

NRTIs, Nucleoside Reverse Transcriptase Inhibitors; NtRTIs, Nucleotide Reverse Transcriptase Inhibitors; yr, years

for use in adolescents ≥ 13 years of age. Three NRTI and one NRTI plus NtRTI co-formulation products are FDA approved (Table 2). Combivir (lamivudine/zidovudine) and Trizivir (abacavir/lamivudine/zidovudine) are approved for use in adolescents but are available only as fixed dose, solid dosage forms. The remaining 2 combination products (Epzicom, abacavir/lamivudine and Truvada, emtricitabine/tenofovir), both of which were recently FDA approved, are not indicated for use in patients <18 years of age.[3] This section will focus on the recently approved NRTI (emtricitabine) and NtRTI (tenofovir) as single-entity products.

Emtricitabine (Emtriva, FTC)

Emtricitabine, a synthetic nucleoside analog, is the most recently approved NRTI. Initially approved on July 7, 2003, for the treatment of HIV-infected adults as part of combination therapy, FTC was recently (September 28, 2005) approved for use in pediatric patients ≥ 3 months of age.[6]

Efficacy

Emtricitabine, a fluorinated derivative of lamivudine (3TC), is phosphorylated intracellularly to the active compound, emtricitabine 5′-triphosphate.[6] Due to the structural similarities of FTC and 3TC these two agents should not be used in combination with one another, as no additive benefit would be seen.[3] The antiviral efficacy of FTC has been proven in vitro and in vivo. In vitro, FTC has consistently shown greater antiviral activity than 3TC.[7] In adult patients, FTC demonstrated significantly greater viral suppression than 3TC in a short-term monotherapy study and displayed antiviral equivalence to 3TC when administered as part of a combination antiretroviral regimen.[8,9] Virologic response to FTC was superior to stavudine (d4T) when either agent was administered in combination with efavirenz (EFV) and enteric-coated didanosine (ddI EC).[10] The efficacy of a once-daily regimen including FTC, ddI EC, and EFV was confirmed in adults both in a pilot study and a randomized, open-label trial.[11,12]

Efficacy of FTC 6 mg/kg once daily in pediatric patients has been reported in 3 abstracts. One non-randomized study replaced 3TC with FTC in 82 patients, both treatment-experienced and treatment-naïve, ages 4 months to 16 years.[13] Evaluation of 47 patients at week 20 demonstrated a viral load < 400 copies/mL in 89% of the patients. The number of patients with virological failure was minimal and comparable in both treatment-naïve and treatment-experienced patients.[13,14] The second study included only minimally treated or treatment-naïve patients.[15] Patients 3–21 years old were assigned to a once-daily regimen including FTC, ddI EC, and EFV. At week 16, preliminary results (n = 23) demonstrated HIV viral loads of < 400 copies/mL in 87% and < 50 copies/mL in 74% of the patients. The third abstract reports the extended follow-up at week 24 for 31 patients of this study.[16] The desired virologic response < 400 copies/mL was achieved in 81% of patients, and 78% reached a viral load < 50 copies/mL. Of the 21 patients who were ≤ 12 years old, 86% demonstrated a

Table 3. Currently Available Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)[3]

Abbreviation	Generic Name (Brand Name)	FDA Approved Age	Formulations
DLV	Delavirdine (Rescriptor)	≥ 16 yr	Tablet: 100 mg, 200 mg
EFV	Efavirenz (Sustiva)	≥ 3 yr	Capsule: 50 mg, 100 mg, 200 mg Tablet: 600 mg
NVP	Nevirapine (Viramune)	≥ 2 mo	Oral suspension: 10 mg/mL Tablet: 200 mg

mo, months; yr, years

viral load < 400 copies/mL, and 81% achieved a viral load < 50 copies/mL. Two patients were permanently withdrawn from this study for treatment failure.

Emtricitabine may have activity against the hepatitis B virus, as it is a structural analog of 3TC. However, the clinical efficacy of FTC against the hepatitis B virus or in HIV-infected patients co-infected with hepatitis B has not been established.[6] Reports of acute exacerbations of hepatitis B have been reported in HIV co-infected patients who have discontinued FTC. Patients co-infected with hepatitis B virus should be monitored closely upon discontinuation of antiretroviral therapy with FTC.

Pharmacokinetics

The pharmacokinetics of FTC have been well described in adults and follow linear elimination. Emtricitabine is rapidly and extensively absorbed.[6] The mean absolute bioavailability is 93% for the capsules but only 75% for the oral solution. Thus, the relative bioavailability of the oral solution compared with the capsule formulation is approximately 80%. While the maximum concentration in the plasma (C_{max}) is decreased when FTC capsules are administered with a high-fat meal, the area-under the plasma concentration-time curve (AUC) is not affected by food. The AUC and C_{max} of the oral solution are not affected by administration with either a low- or high-fat meal. Therefore, FTC may be administered without regard to meals. Peak plasma concentrations are reached within 2 hours following the dose. The current recommended dose of 200 mg once daily, administered as a capsule, produces a C_{max} of 1.8 ± 0.7 μg/mL and AUC of 10.0 ± 3.1 μg•hr/mL following multiple doses. Emtricitabine is not significantly plasma protein bound (4%). The major route of excretion is the kidney, with 86% of the dose recovered in the urine (primarily as unchanged drug) and the remaining 14% eliminated in the feces. Thus, dose adjustment in renal failure is necessary. Renal excretion of FTC is believed to be due to both glomerular filtration and active tubular secretion since the rate of clearance exceeds estimated creatinine clearance. In adults, emtricitabine exhibits a plasma elimination half-life of approximately 10 hours, while its intracellular half-life is approximately 39 hours.

Two studies have evaluated the pharmacokinetics of FTC in pediatric patients. Wang and colleagues evaluated the pharmacokinetics of FTC in 25 pediatric patients < 18 years of age in a phase I, open label, randomized, dose-escalation study.[17] Patients were divided into 5 cohorts based on age (birth to < 3 months; 3 months to < 2 years; 2 years to < 6 years; 6 years to < 13 years; 13 years to < 18 years). Patients received one dose of 60 mg/m^2 of an oral solution (10 mg/mL) and if tolerated, a second dose of 120 mg/m^2 up to a maximum dose of 200 mg. All patients received both doses. Patients in cohorts 4 (6 years to < 13 years) and 5 (13 years to 18 years) could take a second dose as a capsule form of 120 mg/m^2 rounded to the nearest 25 mg with a maximum dose of 200 mg. This study design was used to assess differences in bioavailability between the two dosage forms. Each dose was followed by pharmacokinetic monitoring of both blood and urine. As was seen in the adult studies, FTC followed linear kinetics.[6] Emtricitabine was rapidly and readily absorbed orally when administered either as a capsule or an oral solution. However, slightly higher plasma exposure was seen with the capsule formulation, most likely due to the difference in relative bioavailability. Similar to adults, plasma concentrations of FTC reached the C_{max} within 2 hours of administration. Pharmacokinetic parameters were similar across all age cohorts for both doses. When

Table 4. Currently Available Protease Inhibitors and Fusion Inhibitors[3]

Abbreviation	Generic Name (Brand Name)	FDA Approved Age	Formulations
Protease inhibitors			
APV	Amprenavir (Agenerase)	≥ 4 yr	Oral solution: 15 mg/mL (550 mg propylene glycol/mL and 46 IU of vitamin E/mL) Capsule: 50 mg
ATV	Atazanavir (Reyataz)	≥ 16 yr	Capsule: 100 mg, 150 mg, 200 mg
FPV	Fosamprenavir (Lexiva)	≥ 18 yr	Tablet: 700 mg (equal to 600 mg of APV)
IDV	Indinavir (Crixivan)	≥ 18 yr	Capsule: 100 mg, 200 mg, 333 mg, 400 mg
LPV/RTV	Lopinavir/ritonavir (Kaletra)	≥ 6 mo	Oral solution: 80 mg LPV + 20 mg RTV/mL (42.4% alcohol) Tablet: 200 mg LPV + 50 mg RTV
NFV	Nelfinavir (Viracept)	≥ 2 yr	Powder for oral suspension: 50 mg per 1 level (g) scoopful Tablet: 250 mg, 625 mg
RTV	Ritonavir (Norvir)	> 1 mo	Oral solution: 80 mg/mL (43% alcohol) Capsule: 100 mg
SQV	Saquinavir (Invirase)	> 16 yr	Hard gel capsule (Invirase): 200 mg Tablet (Invirase): 500 mg
TPV	Tipranavir (Aptivus)	≥ 18 yr	Soft gel capsule: 250 mg
Fusion Inhibitors			
T-20	Enfuvirtide (Fuzeon)	≥ 6 yr	Lyophilized powder for injection: 108 mg (concentration following reconstitution – 90 mg/mL)

mo, months; yr, years

given the oral solution, mean AUC for all cohorts ranged from 4.2–4.8 μg•hr/mL with a 60 mg/m^2 dose and 7.7–8.5 μg•hr/mL with a 120 mg/m^2 dose. The capsule formulation dosed at 120 mg/m^2 in cohorts 4 and 5 exhibited a mean AUC range of 8.02–10.93 μg•hr/mL. The mean elimination half-life of the oral solution ranged from 6.43–10.37 hours for the 60 mg/m^2 dose and 9.65–11.93 hours for the 120 mg/m^2 dose. Both apparent and renal clearance seemed to increase with age; however, once clearance was standardized to body surface area it was comparable across all age groups and similar to apparent clearance reported in adults with normal renal function.[6] This study showed that a dose of 120 mg/m^2 produced mean AUCs similar to but slightly less than those seen in both single-dose and multiple-dose adult studies. The authors concluded that a pediatric dose of 120 to 140 mg/m^2 could be chosen to produce similar plasma exposure as seen with a 200 mg dose in adults.

The second pediatric study evaluated the pharmacokinetics of 82 patients 3 months to 17 years of age using a dose of 6 mg/kg once daily; however, the formulation used was not noted.[13] Pharmacokinetic parameters were evaluated at 2 weeks, representing steady state. At the time of abstract publication, 28 patients had been evaluated for preliminary pharmacokinetic results. The authors found a C_{max} similar to that seen in the previous pediatric study and adult studies. Mean AUC seemed to increase moderately with age (1.2 years: 8.1 μg•hr/mL; 5 years: 9.2 μg•hr/mL; 9.8 years: 12.9 μg•hr/mL; 14.8 years: 14.5 μg•hr/mL). Significance of this increase was not reported, and mean AUC values for all age groups were similar to the plasma exposure seen in adults. Elimination half-life ranged from 7.9–9.5 hours; clearance

Table 5. Indications for Initiation of Antiretroviral Therapy in Children with HIV Infection

Clinical Category[a]		CD_4^+ Cell Percentage (Immune Category)[b]		Plasma HIV RNA Copy Number	Recommendation
Children < 12 months of age					
Symptomatic (A, B, or C)	**or**	< 25 % (2 or 3)		Any value[c]	Treat
Asymptomatic (N)	**and**	≥ 25% (1)		Any value[c]	Consider treatment[d]
Children ≥ 12 months of age					
AIDS (C)	**or**	< 15% (3)		Any value	Treat
Mild – Moderate symptoms (A or B)	**or**	15-25%[e] (2)	**or**	≥ 100,000 copies/mL[f]	Consider treatment
Asymptomatic (N)	**and**	≥ 25% (1)	**and**	< 100,000 copies/mL[f]	May defer therapy and monitor clinical, immune, and viral parameters closely

Adapted from: Guidelines for the use of antiretroviral agents in pediatric HIV-infection, November 3, 2005. Available at: http://www.aidsinfo.nih.gov/guidelines.

[a] Clinical categories:

(N) Not symptomatic: Children show no signs or symptoms believed to be attributable to HIV-infection or only one of the symptoms in category A.

(A) Mildly symptomatic: Children with 2 or more of the following: lymphadenopathy; hepatomegaly; splenomegaly; dermatitis; parotitis; recurrent or persistent upper respiratory infections, sinusitis, or otitis media.

(B) Moderately symptomatic: Children with symptomatic conditions considered to be attributable to HIV-infection outside of those listed in categories A and C (e.g., anemia, neutropenia, or thrombocytopenia for ≥ 30 days; bacterial meningitis, pneumonia, or sepsis; candidiasis (oral thrush) > 2 months (in children > 6 months old); cardiomyopathy; cytomegalovirus infection with onset before 1 month of age; recurrent or chronic diarrhea; hepatitis; recurrent herpes simplex virus (HSV) stomatitis; HSV bronchitis, pneumonitis, or esophagitis before 1 month of age; herpes zoster involving more than one dermatome, or 2 distinct episodes; lieomyosarcoma; lymphoid interstitial pneumonia; nephropathy; nocardiosis; fever lasting for > 1 month; toxoplasmosis before 1 month of age; disseminated varicella.)

(C) Severely symptomatic: Patients with an AIDS-defining condition (e.g., Pneumocystis jiroveci pneumonia – PCP) with the exception of lymphoid interstitial pneumonia which is a category B condition.

[b] Immune Categories: CD_4^+ T-cell percentage

(1) No suppression: ≥ 25%

(2) Moderate suppression: 15% to 24%

(3) Severe suppression: < 15%

[c] High HIV RNA levels may not correlate well with disease progression in children < 12 months of age and may be difficult to interpret in this age group.

[d] Since HIV may progress more rapidly in children < 12 months of age some experts would treat all infants regardless of clinical, immunologic, or virologic status.

[e] Many experts would initiate therapy in children with CD_4^+ cell percentages of 15%-20% and defer therapy but closely monitor children with CD_4^+ cell percentage from 21% to 25%.

[f] Controversy exists among pediatric experts on the plasma HIV viral level at which therapy should be initiated, in the absence of clinical or immunologic symptoms; some experts would initiate therapy for viral load ≥ 50,000 copies/mL.

was not reported.

The manufacturer's product labeling reports pharmacokinetic data for 77 pediatric patients ages 3 months to 17 years.[6] Patients received either oral solution (6 mg/kg up to a maximum dose of 240 mg) or capsules (200 mg) once daily. Similar to the previous abstract, parameters were assessed in 4 age cohorts. Both mean AUC and C_{max} (3–24 months: 8.7 μg•hr/mL and 1.9 μg/mL; 25 months–6 years: 9.0 μg•hr/mL and 1.9 μg/mL; 7 years–12 years: 12.6 μg•hr/mL and 2.7 μg/mL; 13 years–17 years: 12.6 μg•hr/mL and 2.7 μg/mL) increased with age. Systemic exposure was similar to adult patients receiving a 200 mg capsule once daily.

Adverse Drug Reactions

In general, FTC was well tolerated in adults during clinical trials. Most adverse reactions reported were mild to moderate in severity.[6,7,14] The most commonly reported adverse reactions in adult patients on combination therapy that

Table 6. Indications for Initiation of Antiretroviral Therapy in Adolescent and Adult Patients with HIV Infection

Clinical Category		CD_4^+ Cell Count		Plasma HIV RNA Copy Number	Recommendation
AIDS-defining illness or severe symptoms[a]	**and**	Any value	**and**	Any value	Treat
Asymptomatic[b]	**and**	< 200 cells/mm^3	**and**	Any value	Treat
Asymptomatic[b]	**and**	>200 cells/mm^3 but ≤ 350 cells/mm^3	**and**	Any value	Treatment should be offered following full discussion of pros and cons with each patient
Asymptomatic[b]	**and**	> 350 cells/mm^3	**and**	≥ 100,000 copies/mL	Most clinicians recommend deferring therapy but some clinicians will treat
Asymptomatic[b]	**and**	> 350 cells/mm^3	**and**	< 100,000 copies/mL	Defer therapy

Adapted from: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents, October 6, 2005. Available at: http://www.aidsinfo.nih.gov/guidelines.
Clinical categories
[a] AIDS-defining illness per CDC 1993
Severe symptoms: patients with unexplained fever or diarrhea for > 2-4 weeks; oral candidiasis; or > 10% unexplained weight loss
[b] Clinical benefit has been shown in controlled studies only for patients with CD_4 T cells < 200 cells/mm^3; however, the majority of clinicians would offer therapy at a CD_4 T cell threshold < 350 cells/mm^3

included FTC were abdominal discomfort, most notably diarrhea and nausea. Also commonly reported were rash, headaches, and nervous system events including depression, insomnia, and paresthesias. A small percentage of patients (3.4%) experienced discoloration of the skin, primarily an increased pigmentation (hyperpigmentation) of palms and soles.[7] This adverse event appears to be unique to FTC and seems to occur predominantly in non-Caucasian patients.[3] In comparator trials, reports of adverse reactions were similar between FTC and 3TC but were less common with FTC compared to d4T.[8-10]

In adults, grade 3 and 4 laboratory abnormalities were also similar to those of 3TC and d4T during combination therapy.[6,7,14] Most common (occurring in > 5% of patients) were increased creatinine kinase, triglycerides, hepatic transaminases, and serum amylase, and decreased neutrophil counts. Cases of lactic acidosis and severe hepatomegaly, including reports of fatality, have been reported with FTC both alone and in combination with other nucleoside analogs.[6] Treatment with FTC should be discontinued in patients who develop clinical or laboratory signs and symptoms consistent with lactic acidosis or hepatic steatosis. Of note, FTC therapy may have favorable effects on high density lipoprotein cholesterol (HDL-C) in adults.[11] When evaluated in combination with ddI EC and EFV and compared with a PI-containing regimen, FTC patients experienced a significantly greater increase in HDL-C with 39% of patients reaching an HDL-C of > 60 mg/dL. However, it is unclear whether this observed difference was secondary to the comparator group receiving PI therapy, which may have negative effects on HDL. Clinicians must also remember that EFV may have adverse effects on serum lipids before completely discounting these results.

Tolerability of FTC in pediatric patients is similar to adults, with the exception of skin discoloration. Hyperpigmentation was reported in 32% of pediatric patients receiving the drug in clinical trials.[6] Of the 29 adverse reactions reported during the dose-escalation pharmacokinetic study, 13 were considered to be drug related.[17] Most frequently reported events included vomiting, diarrhea, abdominal pain, and headache. Few of these events were reported on the day the study drug was administered. Tolerability was similar in 2 other pediatric studies when patients received 6 mg/kg once daily of FTC as a part of combination therapy.[13,15,16]

Table 7. Recommendations for Initial Antiretroviral Therapy in Children

Recommendations	Regimens
Strongly Recommended	2 NRTIs[a] ***plus*** LPV/RTV ***or*** NFV ***or*** RTV Children > 3 yr: 2 NRTIs[a] ***plus*** EFV[b] Children ≤ 3 yr: 2 NRTIs[a] ***plus*** NVP[c]
Alternative Recommendations	2 NRTIs[a] ***plus*** APV (children ≥ 4 yr)[d] ***or*** IDV 2 NRTIs[a] ***plus*** NVP (children > 3 yr)[e] ZDV ***plus*** 3TC ***plus*** ABC
Use in Special Circumstances Only	2 NRTIs[a]
Not Recommended or Insufficient Data	Monotherapy[f] Certain 2 NRTI combinations[a] 2 NRTIs ***plus*** SQV as sole PI[g] 2 NRTIs ***plus*** DLV[h] NRTI ***plus*** NNRTI ***plus*** PI[i] ATV ***or*** FPV ***or*** FTC ***or*** TDF ***or*** TPV ***or*** T-20 containing regimens[h]

Adapted from: Guidelines for the use of antiretroviral agents in pediatric HIV-infection. November 3, 2005. Available at: http://www.aidsinfo.nih.gov/guidelines.

ABC, abacavir; APV, amprenavir; ATV, atazanavir; DLV, delavirdine; EFV, efavirenz; FTC, emtricitabine; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir; TDF, tenofovir; 3TC, lamivudine; TPV, tipranavir; T-20, enfuvirtide; ZDV, zidovudine

[a] Recommendations for NRTI combinations

*Strongly Recommended: ZDV **plus** ddI or 3TC; d4T **plus** 3TC*

*Alternatives: ABC **plus** ZDV or 3TC; ddI **plus** 3TC*

*Use only in special cases: d4T **plus** ddI or ddC **plus** ZDV*

*Not Recommended: ddC **plus** ddI, d4T or 3TC; ZDV **plus** d4T; 3TC **plus** FTC; TDF- or FTC-containing regimens (insufficient data)*

[b] Used with or without NFV; EFV is available in capsule form only

[c] Or those who cannot swallow capsules

[d] APV should not be administered to those < 4 years due to the amount of vitamin E and propylene glycol in the oral solution and the lack of pharmacokinetic data to support its use in this age group

[e] Who are unable to swallow capsules

[f] Exception: ZDV monotherapy when used as prevention for perinatal HIV transmission

[g] SQV (hard and soft-gel capsules) require RTV boosting to achieve appropriate levels in children; however, pharmacokinetic data to establish an appropriate dose of RTV for use with SQV are not available.

[h] Insufficient data

*[i] Insufficient data with the exception of EFV **plus** NFV **plus** 1 or 2 NRTIs, which has been studied and shown to have virologic and immunologic efficacy in children.*

Unlike the dose-escalation pharmacokinetic study, a total of 3 patients withdrew early from these studies because of an adverse event (1 with anemia and 2 with a rash).

No treatment-emergent laboratory toxicity ≥ grade 3 was reported in the pediatric dose-escalation pharmacokinetic study.[17] The most common laboratory toxicities included abnormal hematologic parameters. No patient discontinued this study early due to adverse reactions or laboratory toxicity. Grade 3 and 4 laboratory toxicities were reported in 6.7% and 17% of patients in the other 2 pediatric studies.[13,15] A total of five grade 3 or 4 laboratory toxicities were reported in 37 children in the extended follow-up study of once-daily FTC, ddI EC, and EFV. All of these abnormalities resolved spontaneously and only 3 were considered possibly study drug related.[16] The most current product labeling reports the incidence for any grade 3 or 4 toxicity in pediatric patients as 9% which is less than that reported in adult patients (31% to 34%).[6]

Drug Interactions

Emtricitabine is not metabolized by the cytochrome P450 (CYP450) enzyme system.[6,7,14] In vitro exposure of supratherapeutic concentrations of FTC showed no effects on the pharmacokinetics of drugs metabolized by CYP450. When combined with zidovudine (ZDV), tenofovir disoproxil fumarate (TDF),

Table 8. Recommendations for Initial Antiretroviral Therapy in Adolescents and Adults

Recommendation	Regimen
Preferred Regimen	2 NRTIs / NtRTI[a] ***plus*** EFV[b] 2 NRTIs[c] ***plus*** LPV/RTV[d]
Alternative Recommendations	2 NRTIs[e] ***plus*** EFV[b] 2 NRTIs / NtRTI[f] ***plus*** NVP[g] 2 NRTIs / NtRTI[h] ***plus*** ATV 2 NRTIs / NtRTI[f] ***plus*** FPV ***or*** FPV/r[i] ***or*** IDV/r[i] ***or*** NFV ***or*** SQV[j]/r[i] 2 NRTIs / NtRTI[k] ***plus*** LPV/RTV ZDV ***plus*** 3TC ***plus*** ABC[l]
Not Recommended	Monotherapy 2 NRTIs ABC ***plus***TDF ***plus*** 3TC (or FTC)[m] TDF ***plus*** ddI ***plus*** 3TC (or FTC)[m] TDF ***plus*** ddI ***plus*** NNRTI[n] APV[o] ***or*** DLV ***or*** IDV[p] ***or*** RTV[q] ***or*** SQV[p,r] ***or*** TPV[s] ***or*** T-20-containing regimens ddC ***plus*** ZDV-containing regimens

Adapted from: Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. October 6, 2005. Available at: http://www.aidsinfo.nih.gov/guidelines.

ABC, abacavir; APV, amprenavir; ATV, atazanavir; DLV, delavirdine; ddC, zalcitabine; EFV, efavirenz; FPV, fosamprenavir; FTC, emtricitabine; IDV, indinavir; LPV/RTV, lopinavir / ritonavir; NRTIs, nucleoside reverse transcriptase inhibitors; NtRTI, nucleotide reverse transcriptase inhibitor; NFV, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir ; TDF, tenofovir; 3TC, lamivudine; TPV, tipranavir; T-20, enfuvirtide; ZDV, zidovudine

*[a] Recommended NRTI / NtRTI combinations: 3TC or FTC **plus** ZDV or TDF*

[b] EFV is not recommended for use in the 1st trimester of pregnancy; therefore, EFV is not recommended for females with a high pregnancy potential (i.e., women who want to conceive, women not using effective contraception)

*[c] Recommended NRTI combinations: 3TC or FTC **plus** ZDV – for additional regimens containing LPV/RTV see alternative recommendations*

[d] LPV/RTV co-formulated product (Kaletra)

*[e] Recommended NRTI combinations: 3TC or FTC **plus** ABC or ddI or d4T*

*[f] Recommended NRTI / NtRTI combinations: 3TC or FTC **plus** ZDV or d4T or ddI or ABC or TDF*

[g] Due to the high incidence of asymptomatic hepatic events in women with a CD_4 cell count > 250 cells/mm^3 and men with a CD_4 cell count > 400 cell/mm^3, NVP should not be used unless the benefits clearly out weigh the risk

*[h] Recommended NRTI / NtRTI combinations: 3TC or FTC **plus** ZDV or d4T or ABC or ddI or (TDF plus RTV 100 mg/day)*

[i] Low dose RTV: 100–400 mg/day

[j] Either hard or soft-gel SQV capsules

*[k] Recommended NRTI / NtRTI combinations: 3TC or FTC **plus** d4T or ABC or TDF or ddI*

[l] Only when a preferred or alternative NNRTI or PI based regimen can not be used

[m] High rate of early virologic non-response in treatment-naïve patients.

[n] High rate of early virological failure in treatment-naïve patients

[o] With or without low-dose RTV

[p] Without low-dose RTV

[q] As the sole PI

[r] Soft-gel capsule

[s] With low-dose RTV

indinavir (IDV), d4T, 3TC, ddI, or EFV, these drugs seem to have no discernable effects on the pharmacokinetics of FTC. Theoretically, drugs which compete for renal clearance via the same mechanisms as FTC could interact, altering the clearance of one or both drugs. No clinically significant drug interactions with FTC have been reported.

Pediatric Dosing

Emtricitabine is currently approved for use in the treatment of HIV-1 infection as part of combination therapy in patients ≥ 3 months of age.[6] A pediatric dose of 120 mg/m^2 produced similar but lower mean AUCs compared to adults.[17] However, a dose of 6 mg/kg (as the oral solution) once daily provides comparable systemic exposure to adult patients who receive the 200 mg capsule once daily.[13] Efficacy of FTC in pediatric patients has only been evaluated with a dose of 6 mg/kg once daily.[3,13,15,16] Thus, the FDA approved dose of FTC in pediatric pa-

tients (infants ≥ 3 months of age to adolescents) is 6 mg/kg once daily, administered as the oral solution up to a maximum dose of 240 mg. In pediatric patients > 33 kg, who are able to swallow a solid dosage form, the recommended dose is 200 mg once daily administered as capsules. A once-daily dosing regimen of 200 mg as a capsule or 240 mg of the oral solution is currently recommended for adult patients.

Administration

Emtricitabine is commercially available as 200 mg capsules and a 10 mg/mL oral solution.[6] Emtricitabine oral solution should be stored in the refrigerator prior to dispensing. Once dispensed, the oral solution may be stored at room temperature with an expiration date of 3 months.

Place In Pediatric Therapy

In adults, FTC is a preferred NRTI in combination therapy for the following reasons: excellent antiretroviral potency, durable antiviral response, once-daily dosing, lack of drug interactions, and good tolerability (Table 8).[4] Though recently FDA approved, FTC's place in pediatric therapy has yet to be fully elucidated. The most current pediatric HIV-treatment guidelines have not yet determined FTC's place as part of initial combination therapy (Table 7).[3] Emtricitabine is a feasible once-daily dosing option in pediatric patients especially in those with adherence issues or who require alterations in their current regimen due to virologic failure. Pediatric long-term follow-up safety and efficacy data are needed.

Tenofovir Disoproxil Fumarate (Viread, TDF)

Tenofovir disoproxil fumarate (TDF) is the only currently available NtRTI. Approved by the FDA October 26, 2001, TDF is indicated for use in combination therapy in the treatment of HIV-1 infection.[18] Currently, TDF is approved for use in patients ≥ 18 years of age.

Efficacy

Tenofovir DF is a prodrug of tenofovir, an acyclic nucleotide analog of adenosine 5′-monophosphate.[18] Antiviral efficacy of TDF against HIV-1 has been proven both in vitro and in vivo. In vitro, when tested in both MT-2 T-lymphocytes and peripheral blood mononuclear cells, antiviral potency of TDF exceeds that of tenofovir, most likely due to more rapid intracellular uptake of TDF.[5] Clinical efficacy of TDF, in combination with other antiretrovirals, has been evaluated in adults. Comparable efficacy of TDF and d4T was shown when either drug was administered in combination with 3TC and EFV.[19] In 2 studies of treatment-experienced adults with HIV mutations associated with nucleoside resistance, a significant reduction in HIV RNA was seen when TDF was added to the current antiretroviral regimen (compared with placebo).[20,21] In both studies the virologic response to TDF was deemed to be durable. In a regimen simplification study, patients remained on their current twice-daily antiretroviral regimen or were switched to once-daily TDF, ddI, and NVP.[22] The rates of virologic failure were similar between the 2 groups.

Not all TDF trials in adults have shown favorable efficacy. Early virologic failure has been documented with multiple once-daily antiretroviral regimens containing TDF. In treatment-naïve adults, rates of early virologic failure were high when TDF was combined with ddI EC plus an NNRTI, ddI EC plus 3TC, or abacavir (ABC) plus 3TC.[4,23-27] In one study of treatment-experienced adults with complete virologic suppression, 5 of 8 patients experienced virologic failure when patients were switched to a once-daily regimen of TDF combined with ABC and 3TC.[28] Therefore, the use of these or similar once-daily antiretroviral regimens containing TDF can no longer be recommended (Table 8).[4]

The efficacy of TDF as part of a salvage regimen has been evaluated in 18 heavily treatment-experienced children 8–16 years of age.[29] Tenofovir was dosed using investigational 75 mg tablets, with a target dose of 175 mg/m^2 (actual dose was not reported). Following a 6 day monotherapy pharmacokinetic evaluation, 16 patients were continued on TDF with the addition of an optimized background regimen of other antiretroviral agents. The optimal background regimen was individualized and selected based on each patient's treatment history and drug resistance testing. All 16 patients received a regimen containing a PI plus booster doses of RTV. No significant change in viral load was seen following the 6 days of TDF monotherapy (only 2 subjects achieved a > 0.5 $\log_{10}$ decrease in viral load).

A total of 10 patients experienced a > 0.5 $\log_{10}$ decrease by day 28, and 7 patients maintained this virologic response at both weeks 24 and 48. Median baseline viral load was 5.4 $\log_{10}$. The median viral load decrease from baseline was significant at both weeks 24 (4.96 $\log_{10}$; P = .01) and 48 (4.21 $\log_{10}$; P = .01). Six patients achieved undetectable viral loads (< 400 copies/mL) at weeks 24 and 48, with 4 of the 6 attaining a viral load < 50 copies/mL. The authors caution the reader against drawing strong conclusions about the efficacy of TDF in heavily treatment-experienced children, as this study was designed to provide dosing and safety data. However, the authors conclude that TDF may be effective in treating heavily treatment-experienced children as part of a combination treatment regimen.

Tenofovir DF appears to have activity against hepatitis B.[18] However, the clinical efficacy of TDF against the hepatitis B virus or in co-infected patients has not been evaluated. Reports of acute exacerbations of hepatitis B have been reported in co-infected patients who have discontinued TDF.

Pharmacokinetics

The pharmacokinetics of TDF 300 mg orally once daily are well described in adult patients. Tenofovir DF is a diester prodrug of tenofovir that is absorbed orally.[18] The oral bioavailability of TDF increases when the dose is administered with a high-fat meal, but not with a light meal. Plasma exposure in patients who received multiple oral doses and uncontrolled meal content demonstrated a mean AUC (3324 ± 1370 ng•hr/mL) and C_{max} (326 ± 119 ng/mL) similar to those seen in the fasted state. Time to C_{max} (T_{max}) of TDF is prolonged by approximately 1 hour when administered with food. The current recommendation is that TDF may be administered without regard to meals. Plasma protein binding, documented in vitro, is minimal (0.7%). Renal elimination is via both glomerular filtration and active tubular secretion. Following IV administration 70%–80% of the dose was collected unchanged in the urine within 72 hours. Similar results were seen following the administration of multiple oral doses, with approximately 32% of the dose excreted in the urine over 24 hours. Dose adjustment in patients with moderate or severe renal impairment is required. Tenofovir DF can be removed by hemodialysis, with approximately 10% of a 300 mg dose removed during a 4 hour session.

Pharmacokinetic data in 18 pediatric patients (6.2–16.2 years of age) are available from one open label, multiple dose pharmacokinetic study.[30] The initial target dose of TDF was 175 mg/m^2 administered as 75 mg tablets with the dose rounded to the nearest whole tablet. Due to the constraints of the fixed dose tablet, dosing ranges based on BSA were developed (0.5 m^2 to 0.84 m^2, 150 mg; 0.85 m^2 to 1.29 m^2, 225 mg; ≥ 1.3 m^2, 300 mg). Both single dose and steady-state pharmacokinetics of TDF were analyzed after patients received a moderate-fat breakfast. The median single dose of TDF was 208 mg/m^2 (range, 161 to 256 mg/m^2). Tenofovir DF was rapidly absorbed (T_{max}=1.3 hours). Despite a T_{max} similar to adults, mean TDF AUC (2150 ng•hr/mL) was 34% lower than that seen in adults receiving 300 mg. Renal clearance was 1.5-fold higher than adult values. Patients received combination therapy containing TDF and an optimized background regimen that included at least one PI plus low-dose RTV (booster doses) for 4 weeks prior to the steady-state pharmacokinetic analysis. The median steady-state dose of TDF was 209 mg/m^2/day (range, 158 to 253 mg/m^2/day). Tenofovir DF plasma exposure (C_{max}=302 ng/mL; AUC=2920 ng•hr/mL) was lower but more closely related to adults than following a single dose. Median AUC at steady state was approximately 12% less than adults receiving TDF monotherapy, and median elimination half-life (12.5 hours) was more rapid.[18,30-31] This study demonstrated that a median dose of 209 mg/m^2/day produced a similar but lower median AUC at steady-state compared to adults. This dose is higher than the initial target dose (175 mg/m^2) which was chosen to match most closely with 300 mg once daily dose in adults. Elimination half-life and renal clearance were greater in children and adolescents than in adults. This study was limited to patients who could swallow solid dosage forms, with only one patient < 8 years of age, making it difficult to extrapolate this dosing regimen to pediatric patients of all ages.[30]

Adverse Drug Reactions

Tenofovir DF was generally well tolerated when evaluated in adults.[5,18,31] Most commonly

reported adverse reactions were gastrointestinal complaints (nausea, diarrhea, and flatulence) and dizziness. Reports of adverse reactions associated with mitochondrial toxicity (i.e., peripheral neuropathy) were less common with TDF (6%) when compared to d4T (28%) in combination therapy.[19] Changes in bone mineral density (BMD) of the hip were comparable between TDF and d4T, but changes in biochemical markers associated with bone turnover were significantly higher with TDF. Monitoring bone mineral density and bone turnover in patients with HIV treated with TDF should be considered in patients with a history of pathologic fractures or who are at risk for osteopenia. The incidence of TDF-related renal abnormalities in clinical trials was minimal. However, in postmarketing surveillance TDF-associated renal failure has been reported, including acute renal failure and Fanconi's syndrome.

When compared to d4T, the effects of TDF on lipid profiles were favorable.[5,18] Stavudine was significantly more likely to increase total cholesterol, triglycerides, and low-density lipoproteins.[19] In contrast, TDF was significantly more likely to increase high-density lipoproteins. Other commonly occurring grade 3 and 4 laboratory toxicities included increased creatinine kinase and hepatic transaminases. Total grade 3 and 4 abnormalities were similar between TDF (36%) and d4T (42%).

Tolerability of TDF was assessed in 18 pediatric patients enrolled in a multi-dose pharmacokinetic trial.[30] Patients were assessed for clinical and laboratory toxicities regularly on days 0 to 9 and at week 4. Grade 3 elevations in hepatic transaminases were noted in 2 patients, but resolved following discontinuation of TDF. In both cases, elevated transaminases were noted prior to initiating the study drug (one grade 1 and one grade 2). No other clinically significant laboratory or physical adverse reactions were noted. Tenofovir DF was well tolerated in pediatric patients following 28 days of therapy. In an extension of this trial, tolerability was assessed following 48 weeks of TDF therapy in 16 patients.[29] One patient developed elevated hepatic transaminases which were later attributed to oral contraceptives. Five of fifteen patients assessed at 48 weeks experienced a significant decrease in lumbar spine BMD Z score from baseline. Two of these patients required discontinuation of TDF. Of note, all five of these patients were virologic responders. In addition, all five were Tanner stage 1 (compared to those without decreased Z scores whose Tanner stage was 2.5). A moderately strong correlation between age and decrease in BMD Z scores was documented. Though a decrease in BMD was seen during the 48 week trial, no patients experienced orthopedic fractures. The authors conclude that the loss of BMD may limit the use of TDF in prepubertal children.

Unpublished cases of TDF-induced renal dysfunction in adolescents have been reported.[3] There appears to be a greater risk of this toxicity in patients with lower weight, baseline renal insufficiency, and those receiving concominant nephrotoxins. It is important to monitor renal function of all patients receiving TDF regardless of age.

Drug Interactions

Tenofovir DF is not metabolized by CYP450 enzymes.[5,18,31] However, in vitro, at concentrations much greater than those seen in vivo, TDF mildly inhibited the metabolism of isoenzyme CYP1A.[18] Therefore, the likelihood of drug interactions by this mechanism is low. Co-administration of TDF with ddI leads to a significant increase in ddI peak concentration and AUC. The mechanism of this interaction is unknown but may be due to TDF's inhibition of phosphorolysis of ddI by purine nucleoside phosphorylase.[31] When co-administered with TDF the dose of ddI should be adjusted (e.g., see Videx EC product labeling).[32] Patients receiving TDF in combination with ddI should be monitored closely for emergence of ddI-associated adverse effects, especially pancreatitis and peripheral neuropathy.[5,18,31] Both atazanavir (ATV) and lopinavir/ritonavir (LPV/RTV) have been shown to increase TDF plasma concentrations. This interaction occurs by some unknown mechanism, but is mostly likely due to changes in absorption.[18,31] No dosage adjustment is currently recommended, but patients should be monitored closely for emergence of TDF-associated adverse reactions. Tenofovir DF significantly decreases serum concentrations of ATV (also by an unknown mechanism), which may result in the development of resistance and virologic failure.[18,31] When TDF and ATV

are administered in combination, the addition of low-dose RTV (booster doses) is recommended. Drugs that are excreted renally, via glomerular filtration or active tubular secretion, may compete for elimination with TDF, resulting in increased plasma exposure to one or both drugs.[5,18,31]

Pediatric Dosing

Currently, TDF is not FDA approved for use in patients < 18 years of age. Published data of pediatric patients receiving a median dose of 209 mg/m^2/day showed TDF plasma exposure at steady state less than but similar to adults.[30] Pediatric renal clearance and half-life were quicker compared with adults receiving 300 mg daily. Additionally, due to the fixed dosage form, the age range of patients in this trial was restricted; only one patient < 8 years of age was included. Therefore, trials investigating an alternative dosing regimen (8 mg/kg once daily for children 2 to 8 years and 210 mg/m^2 once daily for children > 8 years) are underway.[3] The recommended dose for patients ≥ 18 years of age is 300 mg once daily.

Administration

Tenofovir DF is currently marketed as a 300 mg tablet only.[3,18] It is important to note that the available TDF tablets are not scored; therefore, accurate splitting of TDF tablets would be difficult and cannot be recommended. A 75 mg tablet and a powder formulation are under investigation.[3] The lack of commercially available pediatric dosage forms significantly limits the use of TDF in pediatrics.

Place In Pediatric Therapy

Tenofovir DF in combination with EFV plus either 3TC or FTC is a preferred initial regimen in adult patients (Table 8) and may be considered for use in adolescents.[4] The optimal dose and efficacy of TDF in pediatric patients of all ages has yet to be established, but clinical trials are underway. Data from these trials as well as long-term follow-up safety data (especially effects on BMD) are needed to fully evaluate TDF's place in pediatric therapy.

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Like the nucleoside analogs (NRTIs / NtRTIs), the NNRTIs inhibit viral replication via inhibition of HIV-1 reverse transcriptase.[3] However, the NNRTIs noncompetitively inhibit viral reverse transcriptase by binding to a unique catalytic site on the enzyme. Similar to the PIs, when used in combination with 2 or more nucleoside analogs, the NNRTIs provide potent antiretroviral activity to a therapeutic regimen. However, resistance to the NNRTIs can develop rapidly and may confer resistance to the entire class of agents.

Currently, 3 FDA approved NNRTIs are available (Table 3).[3,4] All of these agents are approved for pediatric use. However, delavirdine (DLV) is only approved for use in adolescents (≥ 16 years of age) and adults. Nevirapine (NVP) is the only NNRTI available as an oral liquid (Table 3). Efavirenz is the preferred NNRTI as part of initial combination antiretroviral therapy for adults and adolescents.[4] Efavirenz is also strongly recommended as an initial NNRTI in children.[3] However, for children < 3 years of age or those who cannot swallow solid dosage forms, NVP is strongly recommended as initial NNRTI therapy. The use of DLV as part of an initial regimen is not recommended by either the pediatric or adult guidelines (Tables 7 and 8).[3,4] Because these agents have been available for several years, the individual drugs within this class will not be discussed in this article. For a review of these agents the reader is directed to the previous review published in this journal as well as the referenced guidelines.[3,4,33]

Protease Inhibitors (PIs)

In early 1996, introduction of protease inhibitors (PIs) for the treatment of HIV-infection brought about the era of highly active antiretroviral therapy (HAART), now referred to as potent combination antiretroviral therapy.[4] In contrast to both the nucleoside analogs and the NNRTIs, the action of the PIs occurs late in viral replication.[3] The PIs inhibit the viral enzyme protease, which is responsible for cleavage of large viral polyproteins into functional units. Inhibition of protease halts viral replication and prevents the production of mature virions. At therapeutic drug concentrations antiviral activity of the PIs is well documented; however, at subtherapeutic concentrations resistance, including cross-resistance, can

develop rapidly.[3,34]

Protease inhibitor therapy can be associated with several class-related adverse effects.[3] Gastrointestinal discomfort, most notably diarrhea, is commonly reported with the protease inhibitors. Loperamide can be used for patients in whom diarrhea is not tolerable. Metabolic complications such as hyperglycemia, exacerbation of or new onset diabetes mellitus, fat redistribution syndrome, and hyperlipidemia are also observed with PI therapy. Hyperlipidemia can occur in patients of all ages and if left untreated may result in an increased risk of cardiovascular adverse reactions.[3] Patients on PI therapy with hyperlipidemia should be treated and monitored in accordance with the standards of practice and published guidelines.[4,35,36] An increased incidence of spontaneous bleeding with PI therapy has been seen in patients with hemophilia A and B.[3]

The PIs are notorious for causing drug interactions due to alterations of CYP450 metabolism. All PIs are metabolized by CYP450 isoenzyme 3A4.[3] In addition, nelfinavir (NFV) is a substrate of isoenzyme CYP2C19 and ritonavir (RTV) is a substrate of CYP2D6. All currently available PIs inhibit CYP3A4 metabolism. Inhibition of CYP3A4 is not equal among the PIs; inhibition rank order appears to be ritonavir >> indinavir = nelfinavir = amprenavir > saquinavir. Also, atazanavir (ATV) inhibits CYP1A2 and CYP2C8, and RTV inhibits CYP2D6. Ritonavir is an inducer of CYP3A4, 2C9, and 1A2 as well.

Clinically relevant and possibly life-threatening drug interactions may occur when PIs are administered with substrates, inhibitors, or inducers of CYP450 isoenzymes. Inhibition of the CYP450 enzyme system can lead to a decrease in metabolism of CYP450 substrates and an increase in their plasma concentrations, possibly to toxic levels. For example, cisapride, ergot alkaloids, triazolam, midazolam, and pimozide are contraindicated with all of the PIs due to the potential for life-threatening elevations in plasma concentrations of these CYP3A4 substrates.[37,38] Other CYP3A4 substrates (e.g., amiodarone and quinidine) are contraindicated with specific PIs (IDV, NFV, RTV, SQV, and TPV). Due to this same drug interaction, numerous other substrates of CYP3A4 (e.g., lovastatin, simvastatin, and itraconazole) are not recommended for concominant use with any PI. Likewise, drugs which are CYP2D6 substrates, such as propafenone and flecainide, are contraindicated with PIs that inhibit CYP2D6 (e.g., RTV).

Inhibitors of CYP450 isoenzymes can lead to increased plasma concentrations of the PIs which can result in an increased incidence of PI-related adverse reactions and toxicities. When inducers of CYP450 are administered with PIs, plasma exposure of the PI is decreased, possibly to subtherapeutic levels. Exposure to subtherapeutic levels of PIs can lead to the development of viral resistance and treatment failure.[3] The use of some potent CYP3A4 inducers, such as rifampin and St. John's Wort, are not recommended for use with any of the PIs.[37,38] An in depth discussion of drug-drug interactions that may occur with PI therapy is beyond the scope of this article. Within the discussion of each agent, the clinically significant drug interactions with other antiretrovirals and any unique drug interactions will be discussed. Consultation of appropriate references and a comprehensive evaluation of potential drug interactions must occur prior to the initiation of PI therapy.[37,38]

Currently 9 single-entity PIs are FDA approved for the treatment of HIV-infection (Table 4).[3,4] One (lopinavir) is co-formulated with low-dose ritonavir (booster dose) to increase serum concentrations of LPV. Not all of these agents are approved for use in pediatric patients. Six of the currently available agents (amprenavir, atazanavir, lopinavir/ritonavir, nelfinavir, ritonavir, and saquinavir) are approved for use in patients < 18 years of age (Table 4). Only 4 of these 6 agents are commercially available as pediatric dosage forms.[3] Even though options for pediatric dosage forms of PIs exist, poor palability or tolerability may hinder their use. This section will focus on the recently approved PIs including atazanavir, fosamprenavir, lopinavir/ritonavir, and tipranavir.

Atazanavir (Reyataz, ATV)

Atazanavir, a novel azapeptide protease inhibitor, was approved by the FDA on June 20, 2003, for use as part of combination therapy for HIV-1 infection in patients ≥ 16 years of age.[39]

Efficacy

In vitro, ATV is generally more potent than older PIs.[40] Clinical efficacy of ATV has been evaluated in both antiretroviral-naïve and treatment-experienced adults. Two studies have evaluated the efficacy of ATV compared with NFV in antiretroviral-naïve patients.[41,42] Both studies showed similar viral response rates between ATV 400 mg once daily versus NFV (administered either 2 or 3 times a day) as part of combination therapy. One study in treatment-experienced adults showed similar efficacy between once-daily ATV plus saquinavir (SQV) compared to twice-daily SQV plus low-dose RTV when administered as part of combination therapy.[43] Information regarding the antiretroviral efficacy of ATV is not yet available in pediatric patients < 16 years of age.

Pharmacokinetics

The pharmacokinetics of ATV have been evaluated in adult patients using doses of 400 mg once daily and 300 mg once daily (plus low-dose RTV).[39,40] Atazanavir exhibits non-linear kinetics. Atazanavir is rapidly absorbed orally (T_{max} = 2.5 hours). Plasma AUC is increased and pharmacokinetic variation is decreased when ATV is administered with food. The AUC of ATV is increased when a 300 mg dose is administered with low-dose RTV (AUC=46,073 ng•hr/mL); however, in treatment-naïve patients the plasma exposure of a 400 mg dose (AUC = 14,874 ng•hr/mL) without RTV boosting is clinically sufficient. Atazanavir is extensively protein bound to both albumin and α_1-acid glycoprotein (approximately 86%). The extent of ATV's protein binding is not concentration dependent. Atazanavir is extensively metabolized by CYP3A4 and undergoes biliary elimination. Thus, dose adjustments in moderate hepatic impairment are required. The use of ATV in patients with severe hepatic impairment is not recommended. The mean elimination half-life of ATV following a dose of 400 mg is approximately 7 hours.

The pharmacokinetics of ATV in pediatric patients > 3 months of age are currently being evaluated. Initial data is available from one trial evaluating the pharmacokinetics of both RTV-boosted and unboosted ATV.[44] Eligible patients were enrolled into 8 study groups. Study groups 1-4 received ATV without booster-dose RTV, while groups 5-8 received ATV with booster-dose RTV. Groups 5 (91 days to 2 years old) and 6 (> 2 years to 13 years old) received ATV as an investigational powder formulation; groups 7 (> 2 years to 13 years old) and 8 (>13 years to 21 years old) received ATV capsules. The initial dose of ATV was 310 mg/m^2 daily with a maximum dose of 800 mg/day. Ritonavir was dosed at 100 mg/m^2 daily with a maximum of 100 mg/day. Atazanavir dose acceptance criteria were set for AUC (≥ 30 μg•hr/mL with none < 15 μg•hr/mL) and C_{min} (≥ 0.06 μg/mL). If these criteria were not met in 4 of the first 5 patients, the starting dose of ATV was adjusted for the next 5 patients enrolled. Pharmacokinetic data was collected for 24 hours at weeks 1 and 56 and 2 weeks following any pharmacokinetic-guided dose adjustment. Week 1 pharmacokinetic data from 15 patients (119 days to 12.1 years of age) have been reported. The youngest patients [group 5 (91 days to 2 years old)] exhibited the lowest AUC (27.7 μg•hr/mL) and the highest clearance (12.4 L/hr/m^2) when compared to the patients in groups 6 to 8. Overall, the median AUC was 2.8-fold higher in the group with booster-dose RTV (52 μg•hr/mL) compared to the group without booster-dose RTV (18.9 μg•hr/mL). Median clearance was 2.6-fold lower in the group with booster-dose RTV (5.4 L/hr/m^2) compared with the group without booster-dose RTV (14 L/hr/m^2). Further evaluations with ATV plus booster-dose RTV are currently underway to establish the optimal dose in pediatric patients.

Adverse Drug Reactions

In clinical trials, ATV was generally well tolerated in adults. Commonly reported adverse reactions include jaundice, nausea, and headache.[39] In two studies comparing ATV to NFV, the incidence of common adverse effects and the number of patients who discontinued treatment early was similar in both groups, with two exceptions.[41,42] Diarrhea was significantly more common with NVF therapy and jaundice was reported only with ATV therapy. Reports of adverse effects were similar when ATV plus SQV was compared to SQV plus low-dose RTV.[43] Yet, significantly more patients discontinued treatment early due to adverse reactions in the SQV plus low-dose RTV group.

Atazanavir's most notable laboratory abnormality is indirect hyperbilirubinemia, which is reversible upon discontinuation. Reports of hyperbilirubinemia in clinical trials comparing ATV to NFV occurred in the ATV group only.[41,42] Atazanavir inhibits uridine diphosphate glucuronosyl 1A1 (UTG1A1), the enzyme which is responsible for conjugating bilirubin. The inhibition of UTG1A1 is most likely the mechanism by which ATV causes indirect hyperbilirubinemia.[3] This hyperbilirubinemia is isolated and does not seem to be associated with liver failure. Atazanavir appears to result in treatment-emergent dyslipidemias or hyperglycemia less often than the other PIs.[39,40]

Tolerability of ATV is currently being evaluated in pediatric patients. Atazanavir is not recommended in infants < 3 months of age due to the increased risk of kernicterus.[3] One non-randomized, open-label trial assessed the effects of ATV on serum cholesterol and triglycerides in 63 pediatric patients.[45] No significant increases in either serum cholesterol or triglycerides were observed at 24 or 48 weeks.

Drug Interactions

As previously stated, ATV is a substrate of CYP3A4 and an inhibitor of CYP3A4, 2C8, and 1A2.[39,40] In addition, ATV also inhibits metabolism by UGT1A1. Efavirenz, an inducer of CYP3A4, may significantly decrease the AUC of ATV. Ritonavir, a potent CYP3A4 inhibitor, may increase the AUC of ATV. Therefore, when EFV and ATV are administered in combination, low-dose RTV should be added to the regimen. Tenofovir DF decreases plasma concentrations of ATV by an unknown mechanism other than induction of CYP3A4 isoenzymes.[4,39,46] The addition of low-dose RTV is required with concurrent administration of ATV with TDF.

Increases in gastric pH decrease the solubility and bioavailability of ATV.[39] Thus, plasma concentrations are decreased if ATV is administered with antacids, histamine$_2$-receptor blockers (H_2-blockers), proton-pump inhibitors (PPIs), or buffered medications (e.g., ddI buffered tablets). Decreases in plasma concentrations may result in emergence of antiretroviral resistance and virologic failure. The concominant administration of ATV with PPIs is not recommended. Co-administration of ATV with other gastric pH-altering agents requires special administration instructions (see administration section).

Pediatric Dosing

Atazanavir is not currently indicated for use in patients < 16 years of age.[39] Efficacy of ATV has not yet been established in pediatric patients and dosing guidelines are not available.[3] Dosing of ATV in adult patients is based upon whether or not the patient has previously received antiretroviral therapy.[39] Treatment-naïve patients should receive ATV 400 mg once daily while treatment-experienced individuals should receive ATV 300 mg once daily plus low-dose RTV (100 mg once daily). Adolescents ≥ 16 years of age may be treated with ATV using adult dosing guidelines.[4]

Administration

Atazanavir is commercially available as 100 mg, 150 mg, and 200 mg capsules.[39] No pediatric dosage forms are currently marketed for ATV, but a powder formulation is being investigated.[3]

Atazanavir should be administered with food to decrease pharmacokinetic variability and increase plasma concentrations.[39] Since ddI should be administered on an empty stomach, co-administration of these 2 agents requires that ATV be given 2 hours before or 1 hour after ddI. Other buffered medications and antacids should also be separated from ATV by 1 hour prior or 2 hours after the dose. The concominant administration of H_2-blockers and ATV requires that the recommended doses of ATV be administered 2 hours before and 10 hours after the H_2-blocker. Treatment-naïve patients can avoid having to separate these agents by adjusting the ATV dose and combining it with RTV (300 mg ATV plus 100 mg RTV once daily).

Place In Pediatric Therapy

Atazanavir is recommended as part of an alternative initial combination regimen in adults and adolescent patients ≥ 16 years of age (Table 8).[4] Atazanavir should be used with great caution in pediatric patients < 16 years of age. The lack of pharmacokinetic and efficacy data for a dosing regimen, as well as the lack of pediatric dosage forms limits the use of ATV in pediatric patients.

Fosamprenavir (Lexiva, FPV)

Fosamprenavir (FPV), a prodrug of amprenavir (APV), was approved by the FDA on October 20, 2003. Fosamprenavir is indicated for treatment of HIV-infection as part of combination therapy in patients ≥ 18 years of age.[47]

Efficacy

Fosamprenavir is rapidly converted by intracellular phosphatases to APV. All of FPV's antiretroviral activity is due to APV. Therefore, in vitro FPV produces minimal antiretroviral activity due to a lack of available APV.[47,48] Clinical trials in adults have shown very good antiretroviral efficacy with FPV. Fosamprenavir showed similar antiretroviral efficacy to APV in treatment-naïve adults when used in combination with ABC and 3TC.[49] Antiretroviral efficacy of FPV, both once-daily and twice-daily plus low-dose RTV, has been documented in 2 clinical trials of antiretroviral-naïve adults. In both trials FPV was compared with twice-daily NFV when either agent was given as part of combination therapy with ABC and 3TC.[50,51] In one trial, a greater proportion of patients receiving FPV twice daily achieved the desired virologic response when compared with NFV twice daily.[50] In the second trial, the desired antiretroviral response was similar when once-daily FPV plus low-dose RTV was compared with twice-daily NFV; however, more patients in the NFV group experienced virologic failure.[51] The antiretroviral efficacy of FPV has yet to be evaluated in pediatric patients. However, the efficacy of APV, the active component of FPV, is well established in pediatric patients. For a review of APV the reader is directed to the previous review article published in this journal and the referenced guidelines.[3,4,33]

Pharmacokinetics

Fosamprenavir, a phosphate ester prodrug of APV, is highly water soluble and has increased bioavailability compared with APV.[47] Development of FPV allowed for a significant reduction of the pill burden of APV while still providing similar antiretroviral outcomes and pharmacokinetics. Following oral administration, FPV is rapidly hydrolyzed in the gut epithelium to APV and an inorganic phosphate.[48] Thus, minimal FPV is systemically available. The pharmacokinetics of APV, administered as FPV, have been evaluated in adults.[47,48] As expected, mean plasma exposure of APV is greater when low-dose RTV is administered with FPV compared with FPV alone (1400 mg FPV plus 200 mg RTV once daily: AUC 69.4 μg•hr/mL; 700 mg FPV plus 100 mg RTV twice daily: AUC 79.2 μg•hr/mL; 1400 mg FPV twice daily: AUC 33.0 μg•hr/mL). Since plasma exposure is the greatest with twice-daily FPV plus low-dose RTV, this dosing regimen is recommended for PI-experienced patients. Food does not alter the absorption or plasma exposure of FPV; therefore, FPV may be administered without regard to food. Amprenavir is extensively plasma protein bound (90%) to α_1-acid glycoprotein. Following hydrolysis in the gut epithelium, APV is absorbed and extensively metabolized by CYP3A4 to 2 major metabolites. Thus, dose adjustment in hepatic impairment is necessary. The terminal elimination half-life of APV is approximately 7.7 hours. Only a small portion of the dose of FPV is found as unchanged APV in the urine (1%). Thus, the need for dose adjustment in renal impairment is unlikely. The majority of the dose is recovered as 2 major metabolites in the feces (75%) and urine (14%).The pharmacokinetics of FPV in pediatric patients is currently under investigation.[3]

Adverse Drug Reactions

Fosamprenavir is generally well tolerated in adult patients. In clinical trials, the most common treatment-emergent adverse effects reported with FPV were diarrhea, nausea, vomiting, headache, and rash.[47] One case of Stevens-Johnson syndrome has been reported. Fosamprenavir does contain a sulfonamide moiety and should be used with caution in patients with true sulfonamide allergy. Incidence of diarrhea with FPV was significantly less than with NFV when the 2 agents were compared as part of combination therapy.[48,50,51] The incidence of all other reported adverse effects were similar between FPV and NFV. Tolerability of FPV was comparable to that of APV.[49]

The incidence of grade 3 and 4 laboratory abnormalities with FPV therapy was low and comparable to those seen with NFV.[35,36,47,48,51] Following 48 weeks of FPV therapy, a similar proportion of patients in both the FPV and

NFV groups developed clinically significant elevations in LDL cholesterol.

Tolerability data in pediatric patients is not currently available. Evaluation of FPV therapy in pediatric patients is ongoing.[3]

Drug Interactions

Amprenavir is a substrate and inhibitor of CYP3A4.[47,48] Clinically significant drug interactions with other antiretrovirals do exist. Both NVP and EFV decrease concentrations of APV. When NVP or EFV are administered in combination with FPV, the addition of low-dose RTV is required. Recommendations for concomitant EFV and FPV therapy necessitate an increase in low-dose RTV to 300 mg daily. Co-administration of FPV with other PIs may lead to alterations in plasma exposure of APV. Indinavir and NFV increase plasma concentrations of APV, while LPV/RTV and SQV decrease APV plasma exposure. Appropriate dosing for these combinations has not been established, and these combinations are not recommended.

Absorption of FPV may be altered by changes in gastric pH.[47] Histamine$_2$-blockers and PPIs may decrease plasma concentrations of APV and should be used with caution in combination with FPV. Alterations in absorption may lead to decreased plasma concentrations of FPV, development of resistance, and virologic failure.

Pediatric Dosing

Fosamprenavir is not currently FDA approved for use in patients < 18 years of age.[3] The optimal dosing regimen of FPV in pediatric patients is unknown. Studies evaluating the efficacy of FPV plus low-dose RTV both once and twice daily in treatment-naïve and -experienced pediatric patients are ongoing. Dosing of FPV varies based on whether or not the patient is PI-naïve or experienced.[47] PI-naïve patients may receive FPV with or without low-dose RTV. Adult dosing regimens of FPV in PI-naïve patients include 1400 mg twice daily, 700 mg twice daily plus RTV 100 mg twice daily (booster dose), or 1400 mg once daily plus RTV 200 mg once daily (booster dose). In PI-experienced patients the only approved dosing regimen is FPV 700 mg twice daily plus RTV 100 mg twice daily (booster dose).

Administration

Fosamprenavir is commercially available as 700 mg tablets.[47] Each tablet is equivalent to 600 mg of APV. A 50 mg/mL oral suspension is under investigation.[3] Since absorption of APV may be decreased by antacids and buffered medications, FPV should be administered 1 hour after or 2 hours prior to these medications.[47] Fosamprenavir may be administered without regard to meals.

Place In Pediatric Therapy

Fosamprenavir is currently recommended as part of an alternative initial regimen in treatment-naïve adults (Table 8).[4] The use of FPV in adolescents may be considered, especially in light of the discontinuation of APV 150 mg capsules. Adolescent patients successfully treated with APV may be good candidates for FPV therapy, which can reduce the daily pill burden. Use in pediatric patients is limited by a lack of data for an optimal dosing regimen and pediatric dosage forms. Outcomes from the ongoing clinical trials are needed before FPV's place in pediatric therapy can be determined.

Lopinavir/Ritonavir (Kaletra, LPV/RTV)

Lopinavir (LPV) is a PI that is structurally related to ritonavir (RTV). In order to enhance LPV serum concentrations, this PI is available only as a co-formulated product with low-dose RTV (booster-dose).[52,53] Approved by the FDA on September 15, 2000, lopinavir/ritonavir (LPV/RTV) is indicated for treatment of HIV-infected adults and children ≥ 6 months of age.

Efficacy

In vitro, LPV is highly specific for HIV-1 protease and has greater antiretroviral activity than RTV.[53] In vivo, LPV exhibits poor oral bioavailability and is inactivated rapidly during first-pass metabolism by CYP3A4. In an effort to overcome the poor absolute bioavailability of LPV, it is co-formulated with low-dose RTV. Low-dose RTV increases the serum concentration of LPV to adequate levels. Clinical efficacy of LPV/RTV in adults is well established and has been reviewed extensively elsewhere.[53] Briefly, LPV/RTV has been evaluated in treatment-naïve and -experienced adults both in combination with NRTIs and with NRTIs plus NNRTIs with good antiretroviral outcomes.

In one large, double-blind trial, LPV/RTV was compared to NFV when either drug was given in combination with d4T or 3TC.[54] A significantly greater proportion of adult patients in the LPV/RTV group achieved the desired antiretroviral outcomes (i.e., viral load < 400 and < 50 copies/mL). The antiretroviral response to LPV/RTV therapy was deemed durable in a separate open-label, four-year follow-up study.[55] These and other studies supported the elevation of LPV/RTV to the level of preferred PI (above NFV and the other available PIs) in the adult and adolescent treatment guidelines (Table 8).[4]

The clinical efficacy of LPV/RTV has been established in pediatric patients ≥ 6 months of age and is currently under evaluation in younger infants. In a phase I/II open-label trial, 100 pediatric patients (6 months to 12 years), both antiretroviral-naïve and -experienced, received LPV/RTV oral liquid twice daily (initially either LPV/RTV 230/57.5 mg/m^2 or LPV/RTV 300/75 mg/m^2).[56] Treatment-naïve children received LPV/RTV in combination with d4T and 3TC. Treatment-experienced patients received LPV/RTV in combination with NVP plus 1 or 2 NRTIs of the investigator's choice. Following an interim pharmacokinetic analysis at 3 weeks, all patients in the LPV/RTV 230/57.5 mg/m^2 twice-daily group were transitioned to LPV/RTV 300/75 mg/m^2 twice daily. At 48 weeks, the majority of patients (79%) achieved the desired antiretroviral response (viral load < 400 copies/mL). A greater proportion of treatment-naïve patients (84%) achieved the desired level of viral suppression when compared with treatment-experienced patients (75%). Treatment-experienced patients were further stratified by prior PI experience. Treatment-experienced, PI-naïve patients were more likely to achieve a viral load of < 400 copies/mL (88%) when compared with patients with previous PI exposure (58%).[56] Viral RNA continued to be suppressed to the desired level after 72 weeks of therapy. Similar to the results at 48 weeks, a significantly greater proportion of treatment-experienced, PI-naïve patients (81%) continued to have an undetectable viral load after 72 weeks of therapy compared with PI-experienced patients (50%).[53]

One abstract evaluated the efficacy of LPV/RTV plus 2 NRTIs as primary therapy for infants < 6 months of age (n=14).[57] This prospective, open-label trial assessed both LPV/RTV pharmacokinetics and virologic success. The initial dose of LPV/RTV was 300/75 mg/m^2 twice daily with dosage adjustments based on serum concentration determinations (only one infant required a dosage adjustment; see Pharmacokinetic section). Virologic outcomes were defined as success (viral load < 400 copies/mL by week 16), failure (never achieving a viral load < 400 copies/mL), and late suppressors (viral load < 400 copies/mL achieved after week 16). Two infants were withdrawn from the study prior to the 16-week efficacy evaluation. At a median follow up of 50 weeks, 6 of 12 patients (50%) had achieved virologic success. Virologic failure occurred in 2 patients (17%), and 4 patients (34%) were late suppressors (viral load < 400 copies/mL at week 32 to 48). Of the 6 patients not defined as virologic success, 3 were perceived to have failed at 16 weeks due to non-adherence. Non-adherence improved in all three cases with social intervention. These data show an encouraging virologic response to LPV/RTV in infants < 6 months of age; however, further studies are needed to better delineate the optimal dose in this age group.

Once-daily dosing of LPV/RTV is approved for use in treatment-naïve adult patients but not in pediatric patients. One study assessed the efficacy of once-daily LPV/RTV in 14 pediatric patients (1.4 to 12.9 years of age) receiving stable antiretroviral therapy with an undetectable viral load (< 50 copies/mL) for at least 6 months.[58] All patients initially received LPV/RTV 460/115 mg/m^2 once daily in combination with ZDV and 3TC. Three patients required a dosage increase based on serum concentration determinations. After 6 months of once-daily LPV/RTV therapy all 14 children maintained viral loads < 50 copies/mL.

The efficacy of LPV/RTV as part of a salvage regimen for pediatric patients has also been established. In a retrospective observational study, 120 pediatric patients were divided into three cohorts based on treatment.[59] Patients were classified as first-line HAART recipients; PI-experienced, second-line HAART recipients; or PI-experienced, LPV/RTV-containing HAART recipients. A greater proportion of patients in the LPV/RTV-containing HAART cohort (71.5%) achieved the desired virologic

response (viral load < 400 copies/mL) compared to the patients in the first-line HAART cohort (52.4%) and in the second-line HAART cohort (48.3%). Seventy-one of the patients in this study achieved the desired virological response and were followed in a sub-study to assess the likelihood of viral rebound. Patients in the LPV/RTV group were significantly less likely (P = .013) to suffer virological rebound than the PI-experienced patients receiving second-line HAART. A small study in NRTI-resistant pediatric patients (n = 8) showed that a combination of EFV and LPV/RTV, without NRTI therapy, was effective.[60] All patients (7 of 7) who received 48 weeks of therapy achieved a viral load < 400 copies/mL, and 4 of these patients achieved a viral load of < 50 copies/mL. Of note, pharmacokinetic sampling with subsequent dosage adjustment based on plasma levels of LPV was carried out in this study. This practice does not routinely occur in clinical practice making it difficult to extrapolate this data to the pediatric population at large.

Pharmacokinetics

The pharmacokinetics of LPV, administered as LPV/RTV, have been well described in adult patients. However, the absolute bioavailability of LPV, administered as LPV/RTV, has not been established.[52] In adult patients, the mean C_{max} (9.8 μg/mL) is reached approximately 4 hours following administration. The mean AUC of LPV in adult patients receiving LPV/RTV was 92.6 μg•hr/mL.[52] Serum concentrations of LPV were similar for both the capsules and the oral solution when administered in a non-fasting state. However, the AUC and C_{max} were approximately 22% greater with the capsule formulation when administered under fasting conditions. When LPV/RTV is administered with a moderate-fat meal, LPV's AUC is increased by 48% for the capsules and 80% for the oral solution. Administration with a high-fat meal increases LPV's AUC by 97% for the capsules and 130% for the oral solution. Lopinavir/ritonavir should be administered with food to increase bioavailability and decrease pharmacokinetic variation of LPV. Lopinavir is extensively plasma protein bound (98%–99%) to α_1-acid glycoprotein and to albumin (but to a lesser extent). The amount of unbound (free) drug is increased in patients with mild to moderate hepatic impairment.[52] When administered alone, LPV is rapidly and extensively metabolized by CYP3A4. Thus, co-formulation with low-dose RTV is required to achieve adequate LPV serum concentrations.[52,53] The plasma exposure of LPV is increased in patients with mild to moderate hepatic impairment. Although no dosage adjustment is required, clinicians should monitor patients with hepatic impairment closely while receiving therapy with LPV/RTV. The pharmacokinetics of patients with severe hepatic impairment have not been evaluated. There are at least 13 oxidative metabolites of LPV that have been identified in humans. A majority of the LPV dose is excreted in the feces (82.6%) with 19.8% of the dose recovered as unchanged drug. Significantly less of the dose is excreted in the urine (10.4%) with only 2.2% of the dose recovered unchanged. It is unlikely that dosage adjustment in renal failure would be required.[52]

As with adult patients, the pharmacokinetics of LPV, administered as LPV/RTV, have been assessed in children. While mean LPV AUC (72.6 μg•hr/mL) and mean LPV C_{max} (8.16 μg/mL) produced by administration of LPV/RTV at a dose of 230/57.5 mg/m^2 twice daily are less than those in adults, these levels are adequate for antiretroviral efficacy.[52,56] Therefore, a pediatric dose of 230/57.5 mg/m^2, which is considered to be the equivalent of the FDA-approved mg/kg doses, is appropriate.

The pharmacokinetic evaluation of LPV/RTV in pediatric patients < 6 months of age is currently ongoing; preliminary data has recently been reported in abstract from.[57] Fourteen infants received initial doses of LPV/RTV 300/75 mg/m^2 twice daily plus 2 NRTIs. Intensive serum concentration monitoring of LPV/RTV was conducted. Doses of LPV/RTV were adjusted if the 12-hour post-dose serum concentration was < 1 mg/L at week 2, after any dosage adjustment, and at 1 year of age. Median AUC and 12-hour post-dose serum concentration were 64 mg•hr/L and 2.24 mg/L at week 2. Only one infant required dose adjustment. Patients who were classified as virologic success were significantly younger and had a much lower median AUC (34 v 97 mg•hr/L, P = .04) at week 2 compared with virologic non-responders/late responders. Further studies are needed to better delineate age-related pharmacokinetic

differences of LPV/RTV in young infants.

The results from 2 studies that evaluated the pharmacokinetics of once-daily LPV/RTV in pediatric patients are available in abstract form.[58,61] The first study assessed the pharmacokinetics of once-daily LPV/RTV in 14 pediatric patients receiving stable antiretroviral therapy with a viral load < 50 copies/mL for at least 6 months.[58] Patients initially received LPV/RTV in doses of 460/115 mg/m^2 once daily plus ZDV and 3TC. Lopinavir/ritonavir was administered in the morning with food until initial pharmacokinetic sampling was performed on day 14. Following the initial sampling, dosing could be switched to the evening, and additional pharmacokinetic sampling was performed at day 28 and months 2, 3, and 6. Overall, LPV plasma concentrations were similar to those obtained in adults receiving LPV/RTV 800/200 mg once daily. However, inadequate plasma trough concentrations occurred in 3 of 14 patients (C_{min} < 1 mg/L), who then required a dosage increase. Forty-four percent of plasma concentrations were higher when patients received LPV/RTV in the evening compared to values obtained on day 14 (when administered with breakfast). Two of three patients who continued with morning dosing with breakfast had lower plasma values than at day 14. These results underscore the importance of administering once-daily LPV/RTV with a large meal in children in order to obtain adequate serum concentrations.

A second study compared the C_{max} and C_{min} of once- versus twice-daily LPV/RTV in 28 treatment-naïve pediatric patients.[61] Patients received either the standard twice-daily dose of 230/57.5 mg/m^2 (2 patients received 300/75 mg/m^2 because their regimen contained EFV) or a once-daily dose of 460/115 mg/m^2. Lopinavir/ritonavir concentrations were assessed at steady-state with median length of LPV/RTV therapy of 18.5 months. Median C_{min} values were significantly lower (P < .05) in the once-daily group (1.59 mg/L) compared with the twice-daily group (8.85 mg/L). The pharmacokinetic parameters were highly variable and did not correlate with body mass index. The authors concluded that despite the lower C_{min} with once-daily dosing, these concentrations may be sufficient for initial therapy in treatment-naïve children and that pediatric clinical trials of once-daily dosing are warranted.

Adverse Drug Reactions

Tolerability of LPV/RTV is generally similar between adults and children. The most common treatment-emergent adverse effect in adults is diarrhea of mild to moderate severity.[52,53] The incidence of diarrhea was greater for adult patients receiving LPV/RTV once daily as opposed to twice daily. Other somewhat common adverse reactions in adults include abdominal pain, dyspepsia, nausea, and vomiting. Rash has also been reported, and post-marketing reports of Stevens-Johnson Syndrome in adults have occurred. Hepatic dysfunction, including some fatalities, has been reported in patients on combination therapy containing LPV/RTV during post-marketing surveillance. Patients with underlying chronic hepatitis (e.g., patients co-infected with hepatitis B or C) or cirrhosis may be at a greater risk for developing hepatic failure and should be monitored closely when treated with LPV/RTV.

The most common grade 3 or 4 laboratory abnormalities in adults were elevations in hepatic transaminases and amylase.[52,53] In addition, elevations in total cholesterol and triglycerides were commonly seen with LPV/RTV therapy in adults. Of note, serum cholesterol measurements in phase II/III trials of LPV/RTV in adults were obtained without regard to whether the patient was fasting.[53]

Lopinavir/ritonavir is generally well tolerated in children. Similar to adults, the most commonly reported adverse reactions in pediatric patients included diarrhea, vomiting, and taste aversion (the palatability of LPV/RTV oral liquid is poor).[52] Rash has been reported in children as well; moderate to severe rash was reported in 2% of the children involved in the clinical trials. Elevations in hepatic transaminases (AST 8% and ALT 7%) and amylase (7%) were the most common grade 3 and 4 laboratory abnormalities reported in children.

Drug Interactions

Lopinavir is extensively metabolized by CYP3A4. When administered in combination with low-dose RTV, LPV/RTV is an inhibitor of CYP3A4.[52] While RTV is a potent inhibitor of CYP2D6, the co-formulation of LPV/RTV does not inhibit CYP2D6 to a clinically significant level. Thus, CYP2D6 substrates (e.g., propafenone and flecainide) that are contraindicated

with RTV therapy are not contraindicated with the use of LPV/RTV. Efavirenz, NFV, and NVP decrease the plasma concentration of LPV due to induction of CYP3A4. Amprenavir also decreases the plasma concentration of LPV, but by an unknown mechanism. Increased doses of LPV/RTV are recommended for pediatric and adult patients receiving concominant administration of LPV/RTV with APV, EFV, or NVP (please see pediatric dosing section). In adult patients, these same dosage adjustments of LPV/RTV are recommended for concominant use with NFV or FPV; however, recommendations for dose adjustment of LPV/RTV coadministered with NFV or FPV in pediatric patients are not currently available.

Delavirdine may increase plasma concentrations of LPV, but appropriate dosing for this combination has not been established.[52] Lopinavir/ritonavir increases the plasma concentrations of APV, IDV, NFV, and SQV, and doses of these PIs should be decreased as described in the product labeling or in other appropriate references.[37,38,52] The concentrations of both active PIs (i.e., LPV and APV) are decreased when LPV/RTV and FPV are administered in combination. Appropriate dosing for FPV when administered in combination with LPV/RTV is not available for pediatric patients; however, an increased incidence of adverse effects has been reported when these two PI formulations are administered in combination.[52] Co-administration of LPV/RTV with TDF leads to an increase in TDF concentrations through an unknown mechanism.[52] Patients receiving both of these agents should be monitored closely for the emergence of TDF-related adverse reactions and toxicities.

Due to the large concentration of alcohol (42.4%) in the oral solution, co-administration with medications that may cause a disulfiram-like reaction (e.g., disulfiram, metronidazole) is not recommended.[52,53]

Pediatric Dosing

Lopinavir/ritonavir is approved for use in the treatment of HIV infection as part of combination therapy in patients ≥ 6 months of age.[52] Dosing of LPV/RTV in pediatric patients ≥ 6 months of age is well established. Evaluation of dosing in infants < 6 months of age and the use of once-daily dosing in pediatric patients continues to be investigated.[57,58,61]

Of note, the clinical trials which evaluated the efficacy of LPV/RTV in pediatric patients used a mg/m^2 dose, yet the current dosing guidelines are expressed as mg/kg. These mg/kg doses are considered to be the equivalent of the previously tested mg/m^2 doses. The pediatric weight-based dosing of LPV/RTV is separated into 3 dosing cohorts.[52] Patients 7 to < 15 kg should receive 12 mg/kg of LPV twice daily; patients 15–40 kg should receive 10 mg/kg of LPV twice daily; and patients > 40 kg should receive 400 mg of LPV and 100 mg of RTV (5 mL of the oral solution, 3 capsules, or 2 tablets) twice daily. The use of once-daily LPV/RTV in pediatric patients is currently not recommended. The recommended dosing regimen of LPV/RTV in treatment-naïve adults is 400 mg LPV/100 mg RTV (3 capsules or 2 tablets) twice daily or 800 mg LPV/200 mg RTV (6 capsules or 4 tablets) once daily. Only the twice-daily regimen is recommended for treatment-experienced adults.

Increased doses of LPV/RTV are recommended for pediatric and adult patients receiving concominant administration of LPV/RTV with APV, EFV, or NVP.[52] Pediatric patients 7 to < 15 kg should receive LPV 13 mg/kg, and patients 15–45 kg should receive LPV 11 mg/kg administered as LPV/RTV twice daily. Pediatric patients > 45 kg and adults should receive 533 mg LPV/133 mg RTV (4 capsules or 6.5 mL) twice daily. Treatment-naïve patients receiving the tablet formulation do not require dose adjustment; treatment-experienced patients should receive 600 mg LPV/150 mg RTV (3 tablets) twice daily. In adult patients, these same dosage adjustments of LPV/RTV are recommended for concomitant use with NFV or FPV.

Administration

Lopinavir/ritonavir is commercially available as soft gel capsules (133.3 mg LPV/33.3 mg RTV), tablets (200 mg LPV/50 mg RTV) and an oral solution (80 mg LPV/20 mg RTV per 1 mL).[52] As of December 21, 2005, the manufacturer will no longer accept orders for the capsule formulation and patients will have to be transitioned to tablets. This will likely be a disadvantage to some pediatric patients since patients requiring doses smaller than the available tablet size will be required to use

the oral solution.

Both LPV/RTV oral solution and capsules should be administered with food.[52] Administration with food may decrease the absorption of ddI. Therefore, patients on concominant therapy with LPV/RTV oral solution or capsules and ddI should be instructed to separate ddI dosing by 1 hour prior or 2 hours after LPV/RTV. The newly available LPV/RTV tablet may be taken without regard to meals.

Prior to dispensing, the oral solution and the capsules should be refrigerated.[52] After the medication has been dispensed it may be stored at either room temperature or in the refrigerator. If refrigerated, LPV/RTV oral solution and capsules are stable until the manufacturer's expiration date, but if stored at room temperature the medication is only stable for 60 days.

Due to the poor water solubility of LPV/RTV, the oral solution contains a significant amount of alcohol (42.4%).[52] This high concentration of alcohol may cause significant alcohol toxicity including death if accidental ingestion or significant overdose occurs in children.

Place In Pediatric Therapy

The role of LPV/RTV in pediatric and adult HIV therapy is well established. In adult and adolescent patients, LPV/RTV is the preferred PI for initial PI-based combination therapy (Table 8).[4] In pediatric patients, LPV/RTV has documented efficacy and durability of virological response, and is available in a pediatric dosage form. Lopinavir/ritonavir is strongly recommended (as is NFV or RTV) as part of an initial PI-based therapy in combination with 2 preferred NRTIs for children (Table 7).[3]

Tipranavir (Aptivis, TPV)

Tipranavir, a non-peptidic PI, is the most recently approved antiretroviral agent. Approved by the FDA on June 22, 2005, TPV is indicated for treatment of HIV infection as part of combination therapy in highly treatment-experienced patients and in patients who have multiple-PI resistant HIV strains.[62] Currently, TPV is approved for use in patients ≥ 18 years of age.

Efficacy

Tipranavir is the first non-peptidic protease inhibitor. In vitro, antiretroviral efficacy of TPV is preserved against isolates of HIV which are highly resistant to currently available peptidic PIs.[63] Clinical efficacy of TPV in adults has been evaluated and established in comparison with several peptidic PIs. In one study of adults with single-PI experience, TPV plus low-dose RTV was at least as effective as SQV plus low-dose RTV, when either was given as part of combination therapy.[63] Interim analysis of 2 large, ongoing, phase III trials (RESIST-1 and RESIST-2) has shown TPV plus low-dose RTV to be effective.[62] These 2 trials are evaluating the use of TPV plus low-dose RTV compared with traditional PIs (i.e., APV, IDV, LPV, or SQV) plus low-dose RTV in highly treatment-experienced HIV-infected adults. Preliminary results demonstrate that TPV plus low-dose RTV, as part of combination therapy, was significantly more effective than comparator PIs plus low-dose RTV. The efficacy of TPV in pediatric patients has not yet been established.

Pharmacokinetics

The pharmacokinetics of TPV plus low-dose RTV have been evaluated in adult patients. Tipranavir oral absorption is limited and the exact bioavailability is unknown.[62] The mean AUC and C_{max} of TPV plus low-dose RTV is similar between males (710 μM•hr and 77.6 μM) and females (851 μM•hr and 94.8 μM). Administration with a high-fat meal enhances the bioavailability of TPV, but the effect on C_{max} is minimal. Thus, TPV plus low-dose RTV should be administered with food. Tipranavir is a substrate, weak inhibitor, and a potent inducer of P-glycoprotein (P-gp). Due to the induction of P-gp, the trough concentrations of TPV are approximately 70% lower at steady-state compared to those following a single dose. Tipranavir is significantly plasma protein bound (> 99.9%) to both albumin and α_1-acid glycoprotein. Metabolism of TPV occurs predominantly via CYP3A4. Concurrent administration of low-dose RTV, a CYP3A4 inhibitor, significantly reduces TPV clearance and increases TPV plasma concentrations to the desired levels. Thus, low-dose RTV must be administered with TPV therapy. The elimination half-life of TPV administered with low-dose RTV is approximately 6 hours. When administered in combination with low-dose RTV, 82.3% of the dose of TPV is recovered in

the feces, of which 79.9% is unchanged drug. Only 4.4% of the dose is recovered in the urine, of which 0.5% is unchanged drug. Thus, dosage adjustment of TPV in renal failure is not expected to be necessary. The administration of TPV in mild hepatic impairment results in increased TPV serum concentrations but does not require dosage adjustment. The pharmacokinetics of TPV in patients with moderate to severe hepatic impairment have not been evaluated; use of TPV in these patients is currently contraindicated. Currently, pediatric clinical trials of TPV are ongoing. One study will evaluate two doses of TPV in combination with booster dose RTV in pediatric patients 2 to 18 years of age.[3]

Adverse Drug Reactions

Tipranavir is generally well tolerated by HIV-infected adults. In patients receiving TPV plus low-dose RTV, the most commonly reported adverse reactions were diarrhea, nausea, fatigue, headache, and vomiting.[62] Tipranavir contains a sulfonamide moiety and should be used with caution in patients with a true sulfonamide allergy. Clinical hepatitis, hepatic failure, and death have been reported with TPV plus low-dose RTV therapy. Patients with underlying moderate to severe hepatic insufficiency should not receive TPV.[3] Since HIV patients co-infected with hepatitis B or C are at a greater risk for hepatotoxicity, clinicians should exercise great caution when using TPV plus low-dose RTV in these patients.[62] Liver function tests should be obtained at baseline and at regular intervals in all patients receiving TPV therapy. Clinicians and patients should watch closely for signs and symptoms which may be associated with hepatic toxicity (e.g., jaundice, fatigue, nausea, bilirubinuria, hepatomegaly). Mild to moderate rash has also been reported. Rash may be more common in females and may present as an urticaric rash, maculopapular rash, or photosensitivity. The incidence of adverse reactions was similar with TPV plus low-dose RTV compared with comparator PIs plus low-dose RTV therapy. The proportion of patients discontinuing TPV therapy due to adverse reactions was greater than the comparator PIs plus low-dose RTV group, but was not statistically significant.[62] The tolerability of TPV in pediatric patients has not been evaluated.

Overall the incidence of grade 2 to 4 laboratory abnormalities in adults was similar with TPV plus low-dose RTV compared with comparator PIs plus low-dose RTV.[62] However, the incidence of grade 2 to 4 elevations of AST and ALT were greater with TPV therapy. In addition, significantly large elevations in total cholesterol and triglyceride levels were observed with TPV therapy. The incidence of laboratory abnormalities in pediatric patients has not yet been evaluated.

Drug Interactions

Tipranavir is a substrate and inhibitor of CYP3A4, and a substrate, weak inhibitor, and potent inducer of P-gp.[62] Medications which effect drug transport via either induction or inhibition of P-gp may alter TPV concentrations. Inducers of P-gp (e.g., rifampin) may decrease TPV absorption. Therefore, P-gp inducers may decrease plasma exposure of TPV and possibly result in subtherapeutic concentrations and virological failure. Drugs that potently inhibit P-gp (e.g., verapamil) may increase the absorption of TPV leading to increased plasma exposure and possibly an increased incidence of TPV-associated adverse effects and toxicities. Co-administration of TPV plus low-dose RTV with ABC, ddI EC, or ZDV leads to decreased concentrations of these nucleoside analogs. To overcome the interaction between ddI EC and TPV, doses of ddI EC should be separated from TPV plus low-dose RTV by 2 hours. Recommendations for dosage adjustment of ABC or ZDV when co-administered with TPV are not available. Combination of TPV plus low-dose RTV with APV, LPV/RTV, or SQV is not recommended. Tipranavir plus low-dose RTV decreases the plasma concentrations of each of these PIs and recommendations for dosage adjustment are not currently available. Concominant administration of TPV plus low-dose RTV with aluminum- or magnesium-containing antacids may result in decreased TPV bioavailability.

Pediatric Dosing

Tipranavir is currently not indicated for patients < 18 years of age. The efficacy of TPV has not yet been evaluated in pediatric patients, nor is there data to support an optimal dosing

regimen for this age group. The recommended adult dose of TPV is 500 mg twice daily plus 200 mg of RTV twice daily.[62]

Administration

Tipranavir is commercially available only as 250 mg capsules and must be administered with booster doses of RTV.[62] No pediatric dosage forms are currently available but an oral liquid formulation is under investigation.[3] Tipranavir should be administered with food.[62] Since food may decrease the absorption of ddI, patients on concurrent ddI therapy should be instructed to separate the dose of ddI by 1 hour prior or 2 hours after TPV dosing. Since the administration of TPV plus low-dose RTV with antacids may lead to a decrease in TPV plasma concentrations, separation of TPV dosing from antacids should be considered. Tipranavir soft-gel capsules must be stored in the refrigerator prior to opening the bottle.[62] Once the manufacturer's bottle has been opened, the capsules may be stored at room temperature, but expire in 60 days.

Place In Pediatric Therapy

Tipranavir is currently recommended for use in highly treatment-experienced adult patients or in adults with multiple PI-resistant strains of HIV-1.[62] Tipranavir has not been evaluated in treatment-naïve patients and is not currently recommended as part of an initial antiretroviral regimen in adults (Table 8).[4] The use of this new antiretroviral agent in pediatric patients cannot be recommended at this time, due to the lack of data for a dosing regimen or efficacy.

Entry Inhibitors

The number of potential targets for antiretroviral agents has expanded as knowledge of HIV virology has increased.[64] Until recently, antiretroviral agents inhibited viral replication by targeting 1of 2 HIV-specific enzymes, reverse transcriptase or protease. Due to the limitations of the currently available agents in the NRTI/NtRTI, NNRTI, and PI classes, the development of antiretroviral agents with alternative mechanisms of action and improved safety profiles is needed. One such class of agents being explored includes those that inhibit HIV from entering the host cell (entry inhibitors). Several drugs, with various mechanisms of entry inhibition, are being investigated within this class (e.g., attachment inhibitors, co-receptor antagonists, and fusion inhibitors). The fusion of the HIV membrane with a host CD_4 cell and entry into that cell is a complex, multi-step process. HIV transmembrane glycoprotein (gp) 41 and gp 120 as well as heptad repeat regions (HR) 1 and 2 of gp 41 are the major components involved in this process. HIV gp 120 attaches to the CD_4 receptor on the host cell allowing for attachment to a co-receptor. Once gp 120 is bound to the co-receptor, gp 41 undergoes conformational changes allowing for fusion into the cell membrane and the exposure of HR1 and HR2. The proximity of HR1 and HR2 leads to folding of gp 41 into a six-helix bundle, bringing the viral envelope closer to the cell membrane, and allowing for membrane fusion and transfer of viral RNA into the host cell.[64,65] Once inside the host cell, viral RNA is transcribed to DNA and incorporated into the host CD_4 cell DNA; viral peptides are formed, a mature virion is produced, and the host CD_4 cell is destroyed. Therefore, entry inhibitors are able to prevent the infection of the host CD_4 cell and the replication of HIV before it begins.

A fusion inhibitor, enfuvirtide (T-20), is the first FDA approved entry inhibitor (Table 4).[3] Enfuvirtide is the first agent to offer an alternative HIV target and mechanism of action in the treatment of HIV infection in almost a decade. Enfuvirtide prevents the fusion of the HIV envelope to the CD_4 host cell membrane.[65] A synthetic analog of HR2, T-20 is believed to prevent fusion via binding to the HR1 of gp41 and preventing the formation of the six-helix bundle and fusion of the viral membrane to the host cell. By preventing fusion of the viral envelope to the cell membrane, viral RNA does not enter the cell and viral replication is halted. This section will focus on T-20, the only FDA approved entry inhibitor.

Enfuvirtide (Fuzeon, T-20)

Enfuvirtide (T-20) is a 36-amino-acid synthetic peptide which inhibits the fusion of HIV to the host cell.[66] It was approved by the FDA on March 13, 2003, for use as part of combination therapy in HIV-1 infected treatment-experienced patients ≥ 6 years of age,

who have ongoing viral replication in spite of antiretroviral therapy.

Efficacy

The antiviral activity of T-20 has been demonstrated in vitro and is synergistic with other antiretroviral agents.[65] Clinical efficacy of T-20 in treatment-experienced adults failing current antiretroviral therapy has been established. Two large, phase III, randomized, identically designed trials (TORO-1 and TORO-2) compared the efficacy of T-20 plus an optimized background antiretroviral regimen versus a control arm which received an optimized background regimen only.[67,68] Following 24 weeks of therapy, patients (≥ 16 years of age) who received T-20 90 mg twice daily had a significantly greater reduction in viral load. Additionally, the proportion of patients with virologic failure at both 8 and 24 weeks was lower in the patients who received T-20.

Several studies in treatment-experienced children and adolescents ≤ 16 years of age who were failing antiretroviral therapy have shown similar efficacy. In one non-comparator trial, 14 children 4–12 years of age received T-20 at doses of 30 or 60 mg/m^2 twice daily plus a background antiretroviral regimen.[69] After starting T-20, patients remained on their current antiretroviral regimen (background regimen) for the first 7 days of the study. On day 8, the therapy was altered to optimize the background regimen. After the first 7 days of therapy, 11 of the 14 patients had achieved the desired virologic response (a 0.7 $\log_{10}$ reduction in viral load). After 24 weeks of therapy, 6 of 14 patients had a viral load < 400 copies/mL, and 3 of 14 achieved a viral load < 50 copies/mL.[69] Twelve patients in this trial continued beyond the initial 24-week analysis, and 6 of these patients completed the 96-week study.[70] Five of the twelve patients who continued therapy beyond 24 weeks maintained virologic suppression up to the 96-week follow-up point. Two abstracts report clinical outcomes at 24 weeks in children (≥ 5 years of age) and adolescents (≤ 16 years of age) receiving T-20 dosed as 2 mg/kg twice daily plus an optimized background regimen.[71,72] Twenty-eight heavily pretreated adolescents (age 12 to 16 years) were enrolled. After 24 weeks, the viral load decreased by a mean of 0.98 $\log_{10}$.[71] The median decrease in viral load for 24 children (age 5 to 11 years) was 1.53 $\log_{10}$ after 24 weeks of therapy.[72]

Pharmacokinetics

The pharmacokinetics of T-20 have been evaluated in both adult and pediatric patients. In adults, absorption of T-20 following subcutaneous injection was similar for the abdomen, thigh, and arm with an absolute bioavailability of 84.3%.[66] Enfuvirtide is significantly plasma protein bound (92%) mainly to albumin but also to α_1-acid glycoprotein. Mean C_{max} (5.0 μg/mL) was reached approximately 4 hours after the dose. The mean AUC was 48.7 μg•hr/mL in adult patients receiving 90 mg twice daily. Since T-20 is a peptide it is expected that it undergoes catabolism to amino acids. The mean elimination half-life of T-20 is 3.8 hours. A deamidated metabolite is formed when T-20 undergoes hydrogen-independent hydrolysis via nicotinamide adenine dinucleotide phosphate.[65] The deamidated metabolite is approximately 20% as active as the parent compound in vitro. The AUC of the metabolite proportional to the parent compound ranges from 2.4% to 15% in adults. The pharmacokinetics of T-20 have not been evaluated in either hepatic or renal failure patients and dosage adjustment for these patients are not currently available.[66] Of note, the clearance of T-20 is not affected if creatinine clearance is ≥ 35 mL/min. Clearance of T-20 in adult females is 20% lower than adult males after adjusting for body weight. The clearance of T-20 varies in direct proportion to body weight (e.g., clearance decreases in patients with lower body weight). However, no dosage adjustment is required for either sex or body weight in adults.

The pharmacokinetic parameters of T-20 in children and adolescents receiving 2 mg/kg twice daily (maximum dose of 90 mg) is similar to adult patients receiving 90 mg twice daily. Maximum plasma concentrations in children (median C_{max} 6.74 μg/mL) and adolescent patients (median C_{max} 5.70 μg/mL) were similar to those seen in adults.[65,73] This dosing regimen also produced AUCs similar to adults in both children (median AUC 56.9 μg•hr/mL) and adolescent patients (median AUC 43.1 μg•hr/mL). The AUC of the deamidated, active metabolite proportional to the parent compound is approximately 6.3% in children and adolescents, which falls within the adult range.[73]

Adverse Drug Reactions

Injection site reactions were the most common adverse reactions reported by adults receiving T-20.[65,66] Approximately 98% of adults enrolled in the T-20 arm of both TORO trials experienced injection site reactions.[65,67,68] Injection site reactions included swelling, induration, nodule or cyst formation, erythema, pain and discomfort, pruritus, and ecchymosis. Other adverse reactions reported included diarrhea, nausea, vomiting, fatigue, depression, and a possible increased incidence of pneumonia.[65,66] Of note, in adult patients when T-20 plus a background regimen was compared to a background regimen alone, the incidence of diarrhea, nausea, vomiting, and fatigue was similar.[66-68] Hypersensitivity with T-20 therapy has been reported and may re-emerge on re-challenge.[66]

The incidence of laboratory abnormalities was similar for T-20 plus a background regimen compared to a background regimen alone with one exception.[66] Eosinophilia was approximately 3 times more common with T-20 therapy. The clinical significance of this eosinophilia has yet to be clarified.

Three trials have assessed the tolerability of T-20 in pediatric patients followed for 24 weeks. In all 3 of these trials, injection site reactions, mostly mild to moderate in severity, were the most commonly reported adverse reactions (79% to 88%).[69,71,72] One child discontinued treatment with T-20 due to injection aversion.[69] In addition, tolerability data from one trial has been reported at up to 96 weeks of follow-up. Thirty-three percent of the patients in this trial continued to experience injection site reactions of mild to moderate severity between 24 and 96 weeks.[70]

Drug Interactions

Enfuvirtide is not a substrate, inhibitor, or inducer of any of the CYP450 isoenzymes and is not expected to result in any clinically significant drug interactions via this mechanism.[66] No clinically significant drug interactions with any other currently available antiretroviral agents have been identified.

Pediatric Dosing

Enfuvirtide is currently approved for treatment of HIV-infection, as part of combination therapy, in treatment-experienced children ≥ 6 years of age and adults with evidence of ongoing viral replication despite antiretroviral therapy.[66] The safety, efficacy, and pharmacokinetics associated with an optimal dosing regimen have been established in children ≥ 6 years of age, adolescents, and adults. The recommended dosing regimen for patients ≥ 16 years of age is 90 mg (1 mL) twice daily. Patients <16 years of age should receive 2 mg/kg of T-20 twice daily up to a maximum recommended dose of 90 mg twice daily.

Administration

Currently, T-20 is commercially available as a lyophilized powder which must be reconstituted for subcutaneous injection.[66] Enfuvirtide is dispensed in a "convenience kit" consisting of 60 single-dose vials, 60 vials of diluent, 60 diluent syringes, and 60 injection syringes. Each single-dose vial contains 108 mg of T-20. Patients or caregivers should be educated to follow the instructions for reconstitution by adding 1.1 mL of diluent to the vial to obtain a final concentration of 90 mg/mL. Following addition of the diluent, patients or caregivers must wait for complete dissolution of the drug, which may take up to 45 minutes. The vial should not be shaken, as this could denature T-20 since it is a protein. Once the drug is dissolved completely, the dose may be administered or stored in the refrigerator for up to 24 hours in the single dose vial. This allows patients or caregivers to prepare the next dose of medication prior to the time when it is to be administered. However, if stored in the refrigerator the dose should be allowed to return to room temperature prior to administration. It is important to note that for children and small adolescents (i.e., patients < 45 kg) some drug wastage will occur since each single dose vial contains one 90-mg dose. In addition to the instructions required for preparation of the dose, patients and caregivers must receive education on administering subcutaneous injections, site rotation, and universal precautions.

Place In Pediatric Therapy

Currently, T-20 is not recommended for use in treatment-naïve adult or pediatric patients (Tables 7 and 8).[3,4] Enfuvirtide may provide a good option for patients who are failing current

therapy and have few remaining antiretroviral drugs to which their virus is susceptible. The decision to use T-20 requires more consideration than just susceptibility of the virus to the drug and the lack of other treatment options. Patients and caregivers must be accepting of the dosage form to assure that compliance is feasible. Additionally, patients and caregivers must be willing and able to be educated on the appropriate preparation and administration of the medication.

SUMMARY

The mortality and clinical outcomes in children and adolescents with HIV have improved with the expanding options for potent combination antiretroviral therapy. Seven new antiretroviral agents have been introduced since the year 2000. Three of these agents (FTC, LPV/RTV, and T-20) have both FDA approval for use in the treatment of HIV-1 infection in children and adolescents and are commercially available in pediatric dosage forms. Minimal pediatric dosing information has been published for TDF and clinical efficacy in children is being evaluated. Currently, a commercially available pediatric dosage form of TDF does not exist, but 2 new dosage forms, a 75-mg tablet and a powder, are under investigation. An optimal dosing regimen of FPV in pediatric patients has yet to be determined; however, it is important to remember that the safety and efficacy of the active component of FPV (amprenavir) has been established in children and adolescents. Studies of FPV plus low-dose RTV and a FPV oral suspension in pediatric patients are underway. Achieving appropriate serum concentration of ATV in children has been difficult. Currently, the optimal dose of ATV in pediatric patients has yet to be determined. Ongoing trials are evaluating ATV plus low-dose RTV and a powder ATV formulation. Tipranavir is the most recently approved antiretroviral agent and data on its use in children or the development of pediatric dosage forms is not yet available. Continued clinical research of currently available and emerging antiretroviral agents is needed to better expand and optimize drug therapy for pediatric HIV infection.

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