

# TWENTY-EIGHT-YEAR-OLD FEMALE WITH PRIMARY AMENORRHEA AND CHRONIC RENAL FAILURE: A CASE OF FRASIER SYNDROME?

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Frasier syndrome is a very rare developmental disorder of autosomal recessive inheritance. It is characterized by male hermaphroditism, primary amenorrhea, chronic renal failure (CRF), and a number of other abnormalities.

A 28-year-old Nigerian female who was considered as a possible case of Frasier syndrome first presented to us in July 2002 with primary amenorrhea, congenital bilateral absence of middle toes, elevated blood pressure, and the uremic syndrome. The management of the case was mainly conservative, including blood pressure control with appropriate antihypertensives. The problems inherent in this index case are discussed while proffering appropriate management approach in a near-ideal situation, which unfortunately is nonexistent in our local environment. The presentation of this case is informed by the need to create awareness about this rare syndrome being a possible cause of CRF in some of our patients. (*J Natl Med Assoc.* 2004;96:256–261.)

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**Key words:** Frasier syndrome ♦ gonadal dysgenesis ♦ primary amenorrhea ♦ chronic renal failure ♦ syndactyly

## INTRODUCTION

Frasier syndrome (FS) is a very rare human developmental disorder of autosomal recessive inheritance classically affecting 46XY females. It is characterized by male pseudohermaphroditism, primary amenorrhea, cryptophthalmos, syndactyly, genital abnormalities, and chronic renal failure (CRF)<sup>1,2</sup>. This syndrome is associated with the Wilms' tumor gene (WT1), which plays a role in urogenital and gonadal development. Germline mutations of this gene have been observed in

patients with Denys-Drash syndrome (DDS) or FS<sup>3,4</sup>. The WT1 encodes a protein that is believed to exert transcriptional and tumor-suppressor activities. Mutations in this gene have occasionally been associated with Wilms' tumor (<15% of cases) and more consistently with three syndromes characterized by urogenital abnormalities, WAGR (Wilms' tumor, aniridia, genitourinary abnormalities, and mental retardation), DDS, and FS.

In the kidney, WT1 is most highly expressed in glomerular epithelial cells or podocytes, which are essential components of the filtering system.<sup>5</sup> Human subjects heterozygous for point mutations in the WT1 gene, develop renal failure because of the formation of scar tissue within glomeruli.<sup>5</sup>

DDS and FS are related because of mutation in WT1 in both conditions<sup>1,5</sup>. However, they have previously been distinguished by differences in nephropathy. It was found that patients with DDS demonstrated diffuse mesangial sclerosis in contrast to focal and segmental glomerulosclerosis in FS patients<sup>6</sup>. There can be overlap in the clinico-

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pathologic presentation in these two syndromes.

The development of CRF because of parachymatous renal disease in a patient with 46XY gonadal dysgenesis was initially noted by Drash et al.<sup>7</sup> Hauslanden et al. thereafter had described the case of a teenage girl with proteinuria and primary amenorrhea.<sup>8</sup> Haning Jr et al. also had described a case of 46XY gonadal dysgenesis with renal failure. In all of these cases, a uterus, fallopian tube and vagina were present, with a combined gonadoblastoma and dysgerminoma in the streak gonad.<sup>6</sup> However, Melo et al. had described an unusual case of a male with FS with an unusual phenotype, characterized by normal penis size with perineal hypospadias, end-stage renal failure at the age of 19 years, normal adult male serum testosterone levels, paratesticular leiomyoma, unilateral testicular germ-cell tumor, bilateral gonadoblastoma and absence of gonadal dysgenesis.<sup>9</sup> Shimoyama et al. had also reported an association with streak gonads and high risk of gonadoblastoma development in patients with FS.<sup>10</sup>

Karyotyping and gonadal histology are important in making a diagnosis of FS. Gonadal dysgenesis is seen on histology in confirmed cases. Gonadectomy is a preferred modality of treatment once FS is confirmed because of the risk of gonadoblastoma in the streak gonad.

The aim of this communication is to highlight the need for increased awareness of the rather rare syndrome—FS—as a possible cause of CRF amongst our patients.

## CASE REPORT

### Subjective Information

A 28-year-old Nigerian female—a petty trader—presented first to us in the renal unit of the hospital in July 2002 with an eight-week history of recurrent fever, facial and leg swelling, nausea, and vomiting. She was a known hypertensive diagnosed four years prior to presentation, but not a known diabetic. There was a history of significant weight loss, enuresis, weakness and dizziness on erect posture, but no symptoms of cardiac decompensation. She had been amenorrhic since birth. She was married in 1992 but separated because of enuresis and infertility. She admitted having multiple sexual partners after separation from her husband. There was no family history of renal disease. She had laparotomy in 1996 for infertility but was

unsure of the indication for the procedure.

### Objective Physical Findings

Examination revealed a young obese lady who was not in respiratory distress. She was pale but not jaundiced. She had bilateral pitting pedal edema and a congenital absence of both middle toes. Her pulse rate was 108 beats per minute, blood pressure was 170/110 mmHg; apex beat was not displaced. Fundoscopy revealed a grade-2 hypertensive retinopathy. She had minimal ascites but no organomegaly. She was conscious and alert and well oriented in time, place and person, but had asterexis.

### Laboratory Findings

Laboratory investigations revealed proteinuria (2+), many red blood cells and pus cells on urine microscopy, while culture of the mid-stream urine yielded a growth of *Escherichia coli* (*E. coli*) sensitive to ciprofloxacin, ofloxacin, and gentamycin. Blood urea was 65 mg/dl, serum creatinine 10.3 mg/dl, serum potassium 4.4 mEq/L, sodium 138 meq/L, packed cell volume 20%, erythrocyte sedimentation rate 140 mm per hour (westergreen), 24 hour urine protein 5.6 gm and creatinine clearance 7.9 mls per minute. Abdominal ultrasound revealed renal sizes of 9.9 cm by 4.5 cm and 9.7 by 5.5 cm for the left and right kidneys respectively. There was bilateral loss of corticomedullary differentiation. Retroviral screening was positive for HIV-1, but hepatitis B surface antigen reaction was negative.

### Treatment

Blood pressure was controlled with a combination of antihypertensives: tablet nifedipine retard 20 mg twice daily, tablet minizide (prazosin HCl 0.5 mg, polythiazide 0.25 mg) one twice daily, tablet atenolol 50 mg daily. She had appropriate antibiotics for her urinary tract infection and frusemide 100 mg daily for edema control. She had six cycles of peritoneal dialysis and was transfused with two units of packed cells. She also received subcutaneous recombinant erythropoietin 4000 iu twice weekly, but only for a brief period because of the cost implication. She was discharged home after six days on admission and was subsequently managed on an outpatient basis. However, she represented three months later (October 2002) with more generalized edema, breathlessness, and uremic syndrome. Lack of funds precluded her from getting further dialysis treatment, and she died

three days after her re-admission. Autopsy could not be done because the patient's relations failed to give consent.

## DISCUSSION

The differential diagnoses in this case are: CRF secondary to hypertensive nephrosclerosis in an HIV-positive patient, HIV-associated nephropathy (HIVAN), and FS/DDS. Though hypertensive nephrosclerosis is a possibility, the patient did not have displaced apex beat and only had grade-2 hypertensive retinopathy. The observed hypertension in the patient may just have been secondary to the renal pathology. HIVAN is a possibility but for the hypertension, which is not usually a presenting feature of HIVAN. We think that the HIV status may just have been a coincidental pathology. We strongly feel that this patient most probably had FS. She had the majority of the characteristic features of FS—phenotypic female, primary amenorrhea/infertility, syndactyly, and CRF.

Making a definitive diagnosis in this case, like many other cases in this part of the world, was a problem. We were limited by lack of a facility for karyotyping. Also, there was a problem obtaining consent from the patient's relations for tissue biopsy of the kidneys and ovaries for renal and gonadal histology. Another major limitation in the management of this case was the lack of a hemodialysis machine dedicated to dialyzing patients with HIV infection who have indications for hemodialysis. Therefore, the only option left for dialyzing such patients is peritoneal dialysis, which is intermittent (no facility for ambulatory peritoneal dialysis) and more expensive than hemodialysis in our center, with its attendant complications, especially infection. We hope that in the future, this category of patients will be better managed with improved facilities and better patient awareness.

There is enough evidence to show that there is risk of gonadal malignancy in phenotypic female patients presenting with primary amenorrhea and CRF. We therefore recommend that:

- Serum follicle stimulating hormone (FSH) level should be measured in any patient presenting with primary amenorrhea.
- Gonadectomy should be performed in all cases of XY gonadal dysgenesis.
- Gonadal dysgenesis should be considered in any female with renal disease and pubertal delay or primary amenorrhea.

## ACKNOWLEDGEMENT

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### Indication

KALETRA is indicated in combination with other antiretroviral agents for the treatment of HIV infection. This indication is based on analyses of plasma HIV RNA levels and CD<sub>4</sub> cell counts in controlled studies of KALETRA of 48 weeks duration and in smaller, uncontrolled dose-ranging studies of KALETRA of 72 weeks duration.<sup>2</sup>

### Safety Information

- Kaletra should not be given to patients who have had an allergic reaction to KALETRA (lopinavir/ritonavir) or any of its ingredients. KALETRA is contraindicated with astemizole, cisapride, dihydroergotamine, ergonovine, ergotamine, flecainide, methylergonovine, midazolam, pimozide, propafenone, terfenadine or triazolam. KALETRA should not be co-administered with lovastatin, simvastatin, St. John's wort (*Hypericum perforatum*) or rifampin.<sup>2</sup>
- Concomitant use with sildenafil is expected to substantially increase sildenafil concentrations and may increase sildenafil-associated adverse events, including hypotension, syncope, visual changes, and prolonged erection.<sup>2</sup>
- Pancreatitis, including some fatalities, has been observed in patients receiving KALETRA.<sup>2</sup>

- Caution should be exercised when administering KALETRA to patients with hepatic impairment including those with hepatitis B or C or marked elevations in transaminases. There have been reports of hepatic dysfunction, including some fatalities. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment.<sup>2</sup>
- Treatment with KALETRA has resulted in large increases in total cholesterol and triglycerides, which should be monitored before and during therapy.<sup>2</sup>
- In patients receiving PIs, increased bleeding (in patients with hemophilia), new onset or exacerbation of diabetes mellitus, and hyperglycemia have been reported.<sup>2</sup>
- Various degrees of cross-resistance among protease inhibitors have been observed.<sup>2</sup>
- Redistribution and accumulation of body fat has been reported in patients receiving ARV therapy. A causal relationship has not been established.<sup>2</sup>
- In KALETRA clinical trials, the most common adverse events of moderate to severe intensity reported in ≥2% of patients were abdominal pain, asthenia, diarrhea, headache, nausea and vomiting.<sup>2</sup>

\*KALETRA + 3TC + (d4T or AZT) is the only preferred PI-based regimen for initial therapy.

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Please see brief summary of Prescribing Information on adjacent page.

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**BRIEF SUMMARY**

**CONSULT PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION**

**KALETRA®**

(lopinavir/ritonavir) capsules

(lopinavir/ritonavir) oral solution

**CONTRAINDICATIONS:** KALETRA is contraindicated in patients with known hypersensitivity to any of its ingredients, including ritonavir.

Co-administration of KALETRA is contraindicated with drugs that are highly dependent on CYP3A or CYP2D6 for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events. These drugs are listed in Table 1.

**Table 1: Drugs That Are Contraindicated With KALETRA**

Drug Class	Drugs Within Class That Are Contraindicated With KALETRA
Antiarrhythmics	Flecainide, Propafenone
Antihistamines	Astemizole, Terfenadine
Ergot Derivatives	Dihydroergotamine, Ergonovine, Ergotamine, Methylergometrine
GI motility agent	Cisapride
Neuroleptic	Pimozide
Sedative/hypnotics	Midazolam, Triazolam

**WARNINGS: ALERT: Find out about medicines that should NOT be taken with KALETRA.** This statement is included on the product's bottle label.

**Drug Interactions:** KALETRA is an inhibitor of the P450 isozyme CYP3A. Co-administration of KALETRA and drugs primarily metabolized by CYP3A or CYP2D6 may result in increased plasma concentrations of the other drug that could increase or prolong its therapeutic and adverse effects (see **CONTRAINDICATIONS - Table 1: Drugs That Are Contraindicated With KALETRA, PRECAUTIONS - Table 2: Drugs That Should Not Be Co-administered With KALETRA and Table 3: Established and Other Potentially Significant Drug Interactions**).

Particular caution should be used when prescribing sildenafil in patients receiving KALETRA. Co-administration of KALETRA with sildenafil is expected to substantially increase sildenafil concentrations and may result in an increase in sildenafil-associated adverse events including hypotension, syncope, visual changes and prolonged erection (see **PRECAUTIONS: Drug Interactions** and the complete prescribing information for sildenafil).

Concomitant use of KALETRA with lovastatin or simvastatin is not recommended. Caution should be exercised if HIV protease inhibitors, including KALETRA, are used concurrently with other HMG-CoA reductase inhibitors that are also metabolized by the CYP3A4 pathway (e.g., atorvastatin). The risk of myopathy, including rhabdomyolysis may be increased when HIV protease inhibitors, including KALETRA, are used in combination with these drugs.

Concomitant use of KALETRA and St. John's wort (*Hypericum perforatum*), or products containing St. John's wort, is not recommended. Co-administration of protease inhibitors, including KALETRA, with St. John's wort is expected to substantially decrease protease inhibitor concentrations and may result in sub-optimal levels of lopinavir and lead to less of virologic response and possible resistance to lopinavir or to the class of protease inhibitors.

**Pancreatitis:** Pancreatitis has been observed in patients receiving KALETRA therapy, including those who developed marked triglyceride elevations. In some cases, fatalities have been observed. Although a causal relationship to KALETRA has not been established, marked triglyceride elevations is a risk factor for development of pancreatitis (see **PRECAUTIONS - Lipid Elevations**). Patients with advanced HIV disease may be at increased risk of elevated triglycerides and pancreatitis, and patients with a history of pancreatitis may be at increased risk for recurrence during KALETRA therapy.

**Pancreatitis should be considered if clinical symptoms (nausea, vomiting, abdominal pain) or abnormalities in laboratory values (such as increased serum lipase or amylase values) suggestive of pancreatitis should occur. Patients who exhibit these signs or symptoms should be evaluated and KALETRA and/or other antiretroviral therapy should be suspended as clinically appropriate.**

**Diabetes Mellitus/Hyperglycemia:** New onset diabetes mellitus, exacerbation of pre-existing diabetes mellitus, and hyperglycemia have been reported during postmarketing surveillance in HIV-infected patients receiving protease inhibitor therapy. Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for treatment of these events. In some cases, diabetic ketoacidosis has occurred. In those patients who discontinued protease inhibitor therapy, hyperglycemia persisted in some cases. Because these events have been reported voluntarily during clinical practice, estimates of frequency cannot be made and a causal relationship between protease inhibitor therapy and these events has not been established.

**PRECAUTIONS: Hepatic Impairment and Toxicity**

KALETRA is principally metabolized by the liver; therefore, caution should be exercised when administering this drug to patients with hepatic impairment, because lopinavir concentrations may be increased. Patients with underlying hepatitis B or C or marked elevations in transaminases prior to treatment may be at increased risk for developing further transaminase elevations or hepatic decompensation. These have been postmarketing reports of hepatic dysfunction, including some fatalities. These have generally occurred in patients with advanced HIV disease taking multiple concomitant medications in the setting of underlying chronic hepatitis or cirrhosis. A causal relationship with KALETRA therapy has not been established. Increased AST/ALT monitoring should be considered in these patients, especially during the first several months of KALETRA treatment.

**Resistance/Cross-resistance:** Various degrees of cross-resistance among protease inhibitors have been observed. The effect of KALETRA therapy on the efficacy of subsequently administered protease inhibitors is under investigation.

**Hemophilia:** There have been reports of increased bleeding, including spontaneous skin hematomas and hemarthrosis, in patients with hemophilia type A and B treated with protease inhibitors. In some patients additional factor VIII was given. In more than half of the reported cases, treatment with protease inhibitors was continued or reintroduced. A causal relationship between protease inhibitor therapy and these events has not been established.

**Fat Redistribution:** Redistribution/accumulation of body fat including central obesity, dorsocervical fat enlargement (buffalo hump), peripheral wasting, facial wasting, breast enlargement, and "cushingoid" appearance

have been observed in patients receiving antiretroviral therapy. The mechanism and long-term consequences of these events are currently unknown. A causal relationship has not been established.

**Lipid Elevations:** Treatment with KALETRA has resulted in large increases in the concentration of total cholesterol and triglycerides (see **ADVERSE REACTIONS - Table 5**). Triglyceride and cholesterol testing should be performed prior to initiating KALETRA therapy and at periodic intervals during therapy. Lipid disorders should be managed as clinically appropriate. See **PRECAUTIONS Table 3: Established and Other Potentially Significant Drug Interactions** for additional information on potential drug interactions with KALETRA and HMG-CoA reductase inhibitors.

**Information for Patients:** A statement to patients and health care providers is included on the product's bottle label: "ALERT: Find out about medicines that should NOT be taken with KALETRA." A Patient Package Insert (PPI) for KALETRA is available for patient information.

Patients should be told that sustained decreases in plasma HIV RNA have been associated with a reduced risk of progression to AIDS and death. Patients should remain under the care of a physician while using KALETRA. Patients should be advised to take KALETRA and other concomitant antiretroviral therapy every day as prescribed. KALETRA must always be used in combination with other antiretroviral drugs. Patients should not alter the dose or discontinue therapy without consulting with their doctor. If a dose of KALETRA is missed patients should take the dose as soon as possible and then return to their normal schedule. However, if a dose is skipped the patient should not double the next dose.

Patients should be informed that KALETRA is not a cure for HIV infection and that they may continue to develop opportunistic infections and other complications associated with HIV disease. The long-term effects of KALETRA are unknown at this time. Patients should be told that there are currently no data demonstrating that therapy with KALETRA can reduce the risk of transmitting HIV to others through sexual contact.

KALETRA may interact with some drugs; therefore, patients should be advised to report to their doctor the use of any other prescription, non-prescription medication or herbal products, particularly St. John's wort.

Patients taking didanosine should take didanosine one hour before or two hours after KALETRA.

Patients receiving sildenafil should be advised that they may be at an increased risk of sildenafil-associated adverse events including hypotension, visual changes, and sustained erection, and should promptly report any symptoms to their doctor.

Patients receiving estrogen-based hormonal contraceptives should be instructed that additional or alternate contraceptive measures should be used during therapy with KALETRA.

KALETRA should be taken with food to enhance absorption. Patients should be informed that redistribution or accumulation of body fat may occur in patients receiving antiretroviral therapy and that the cause and long term health effects of these conditions are not known at this time.

**Drug Interactions:** KALETRA is an inhibitor of CYP3A (cytochrome P450 3A) both in vitro and in vivo. Co-administration of KALETRA and drugs primarily metabolized by CYP3A (e.g., dihydropyridine calcium channel blockers, HMG-CoA reductase inhibitors, immunosuppressants and sildenafil) may result in increased plasma concentrations of the other drugs that could increase or prolong their therapeutic and adverse effects (see **Table 3: Established and Other Potentially Significant Drug Interactions**). Agents that are extensively metabolized by CYP3A and have high first pass metabolism appear to be the most susceptible to large increases in AUC (1-3-fold) when co-administered with KALETRA.

KALETRA inhibits CYP2D6 in vivo, but to a lesser extent than CYP3A. Clinically significant drug interactions with drugs metabolized by CYP2D6 are possible with KALETRA at the recommended dose, but the magnitude is not known. KALETRA does not inhibit CYP2C8, CYP2C19, CYP2E1, CYP2B6 or CYP1A2 at clinically relevant concentrations. KALETRA has been shown in vivo to induce its own metabolism and to increase the biotransformation of some drugs metabolized by cytochrome P450 enzymes and by glucuronidation.

KALETRA is metabolized by CYP3A. Co-administration of KALETRA and drugs that induce CYP3A may decrease lopinavir plasma concentrations and reduce its therapeutic effect (see **Table 3: Established and Other Potentially Significant Drug Interactions**). Although not noted with concurrent ketoconazole, co-administration of KALETRA and other drugs that inhibit CYP3A may increase lopinavir plasma concentrations.

Drugs that are contraindicated and/or not recommended for co-administration with KALETRA are included in **Table 2: Drugs That Should Not Be Co-administered With KALETRA**. These recommendations are based on either drug interaction studies or predicted interactions due to the expected magnitude of interaction and potential for serious events or loss of efficacy.

**Table 2: Drugs That Should Not Be Co-administered With KALETRA**

Drug Class: Drug Name	Clinical Comment
Antiarrhythmics: flecainide, propafenone	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antihistamines: astemizole, terfenadine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Antimycobacterial: rifampin	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors or other co-administered antiretroviral agents.
Ergot Derivatives: dihydroergotamine, ergonovine, ergotamine, methylergometrine	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as acute ergot toxicity characterized by peripheral vasospasm and ischemia of the extremities and other tissues.
GI Motility Agent: cisapride	CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as cardiac arrhythmias.
Herbal Products: St. John's wort ( <i>Hypericum perforatum</i> )	May lead to loss of virologic response and possible resistance to KALETRA or to the class of protease inhibitors.
HMG-CoA Reductase Inhibitors: lovastatin, simvastatin	Potential for serious reactions such as risk of myopathy including rhabdomyolysis.
Neuroleptic: pimozide	CONTRAINDICATED due to the potential for serious and/or life-threatening reactions such as cardiac arrhythmias.

Sedative/Hypnotics:  
midazolam, triazolam

CONTRAINDICATED due to potential for serious and/or life-threatening reactions such as prolonged or increased sedation or respiratory depression.

**Table 3: Established and Other Potentially Significant Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Studies or Predicted Interaction**

Concomitant Drug Class: Drug Name	Effect on Concentration of Lopinavir or Concomitant Drug	Clinical Comment
HIV-Antiretroviral Agents		
Non-nucleoside Reverse Transcriptase Inhibitors: efavirenz, nevirapine	↑ Lopinavir	A dose increase of KALETRA to 500/300 mg (4 capsules or 0.5 mL) twice daily taken with food is recommended when used in combination with efavirenz or nevirapine. <b>NOTE:</b> Efavirenz and nevirapine reduce the activity of CYP3A and thus have the potential to decrease plasma concentrations of other protease inhibitors when used in combination with KALETRA.
Non-nucleoside Reverse Transcriptase Inhibitor: didanosine	↑ Lopinavir	Appropriate dose of the combination with respect to safety and efficacy have not been established.
Nucleoside Reverse Transcriptase Inhibitor: didanosine		It is recommended that didanosine be administered on an empty stomach; therefore, didanosine should be given one hour before or two hours after KALETRA (given with food).
HIV-Protease Inhibitors: amprenavir, nelfinavir, saquinavir	When co-administered with reduced doses of concomitant protease inhibitors: ↑ Amprenavir (Similar AUC, $C_{max}$ , $T_{max}$ ) ↑ Nelfinavir (Similar AUC, $C_{max}$ , $T_{max}$ ) ↑ Saquinavir (Similar AUC, $T_{max}$ )	Alterations in concentrations (e.g., AUC, $C_{max}$ and $T_{max}$ ) are noted when reduced doses of concomitant protease inhibitors are co-administered with KALETRA. Appropriate doses of co-administration with respect to safety and efficacy have not been established.
HIV-Protease Inhibitor: atazanavir	↑ Lopinavir	Appropriate doses of atazanavir in combination with KALETRA with respect to safety and efficacy have not been established.
Other Agents		
Antiarrhythmics: amiodarone, bepridil, flucicaine (cystemic), and quinidine	↑ Antiarrhythmics	Caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when co-administered with KALETRA, if available.
Anticoagulant: warfarin		Concentrations of warfarin may be affected. It is recommended that INR (international normalized ratio) be monitored.
Anticancer: carbamazepine, phenytoin, phenylethynolone	↑ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Antiviral: dantrolene	↑ Dantrolene	For patients with renal impairment, the following dosage adjustments should be considered: • For patients with CrClR 30 to 60 mL/min the dose of dantrolene should be reduced by 50%. • For patients with CrClR <30 mL/min the dose of dantrolene should be decreased by 75%. No dose adjustment for patients with normal renal function is necessary.
Antifungal: itraconazole, itraconazole	↑ Itraconazole ↑ Itraconazole	High doses of itraconazole or itraconazole (>200 mg/day) are not recommended. (Dose reduction of itraconazole by at least 75% of the oral dose of 200 mg/day is recommended (i.e., a maximum dose of 150 mg every other day or three times per week). Increased monitoring for adverse events is warranted in patients receiving the combination. Further dosage reduction of itraconazole may be necessary.
Antibiotic: clarithromycin	↑ Clarithromycin	Clinical significance is unknown; however, increase in clarithromycin dose may be needed.
Calcium Channel Blocker: Dihydropyridine: e.g., isradipine, nifedipine, nitrendipine	↑ Dihydropyridine calcium channel blockers	caution is warranted and clinical monitoring of patients is recommended.
Cardiovascular: Dexamethasone	↑ Lopinavir	Use with caution. KALETRA may be less effective due to decreased lopinavir plasma concentrations in patients taking these agents concomitantly.
Diuretic/retinoid: acetazolamide		KALETRA oral solution contains alcohol, which can produce diuretic-like actions when co-administered with diuretic or other drugs that produce the diuretic effect (e.g., acetazolamide).
Enzyme Inducer: St. John's wort	↓ Lopinavir	Use with caution at reduced doses of 25 mg every 12 hours with increased monitoring for adverse events.
HMG-CoA Reductase Inhibitor: atorvastatin	↓ Atorvastatin	Use lowest possible dose of atorvastatin with careful monitoring, or consider other HMG-CoA reductase inhibitors such as pravastatin or fluvastatin in combination with KALETRA.
Immunosuppressant: cyclosporine, tacrolimus, sirolimus	↑ Immunosuppressant	Therapeutic concentration monitoring is recommended for immunosuppressant agents when co-administered with KALETRA.
Neuroleptic: Mefloquine	↑ Mefloquine	Dosage of mefloquine may need to be increased when co-administered with KALETRA.
Oral Contraceptive: ethinylloestradiol	↓ Ethinylloestradiol	Alternative or additional contraceptive measures should be used when estrogen-based oral contraceptives and KALETRA are co-administered.

**Other Drugs:** Drug interaction studies reveal no clinically significant interaction between KALETRA and pravastatin, stavudine or lamivudine. Based on known metabolic profiles, clinically significant drug interactions are not expected between KALETRA and fluoxetine, dapsone, trimethoprim/sulfamethoxazole, azithromycin, erythromycin, or fluazecol.

Zidovudine and Abacavir: KALETRA induces glucuronidation; therefore, KALETRA has the potential to reduce zidovudine and abacavir plasma concentrations. The clinical significance of this potential interaction is unknown.

**Carcinogenesis, Mutagenesis and Impairment of Fertility:** Long-term carcinogenicity studies of KALETRA in animal systems have not been completed.

Carcinogenicity studies in mice and rats have been carried out on raltegravir. In male mice, at levels of 50, 100 or 200 mg/kg/day, there was a dose dependent increase in the incidence of both adenomas and combined adenomas and carcinomas in the liver. Based on AUC measurements, the exposure at the high dose was approximately 4-fold for males that of the exposure in humans with the recommended therapeutic dose (400/100 mg KALETRA BID). There were no carcinogenic effects seen in females at the dosages tested. The exposure at the high dose was approximately 9-fold for the females that of the exposure in humans. In rats dosed at levels of 7, 15 or 30 mg/kg/day there were no carcinogenic effects. In this study, the exposure at the high dose was approximately 0.7-fold that of the exposure in humans with the 400/100 mg KALETRA BID regimen. Based on the exposures achieved in the animal studies, the significance of the observed effects is not known. However, neither lopinavir nor ritonavir was found to be mutagenic or clastogenic in a battery of *in vitro* and *in vivo* assays including the Ames bacterial reverse mutation assay using *S. typhimurium* and *E. coli*, the mouse lymphoma assay, the mouse micronucleus test and chromosomal aberration assays in human lymphocytes.

Lopinavir in combination with ritonavir at a 2:1 ratio produced no effects on fertility in male and female rats at levels of 10/5, 30/15 or 100/50 mg/kg/day. Based on AUC measurements, the exposures in rats at the high doses were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir of the exposures in humans at the recommended therapeutic dose (400/100 mg BID).

**Pregnancy:** Pregnancy Category C: No treatment-related malformations were observed when lopinavir in combination with ritonavir was administered to pregnant rats or rabbits. Embryonic and fetal developmental toxicities (early resorption, decreased fetal viability, decreased fetal body weight, increased incidence of skeletal variations and skeletal ossification delays) occurred in rats at a maternally toxic dosage (100/50 mg/kg/day). Based on AUC measurements, the drug exposures in rats at 100/50 mg/kg/day were approximately 0.7-fold for lopinavir and 1.8-fold for ritonavir for males and females that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). In a peri- and postnatal study in rats, a developmental toxicity (a decrease in survival in pups between birth and postnatal day 21) occurred at 40/20 mg/kg/day and greater.

No embryonic and fetal developmental toxicities were observed in rabbits at a maternally toxic dosage (80/40 mg/kg/day). Based on AUC measurements, the drug exposures in rabbits at 80/40 mg/kg/day were approximately 0.6-fold for lopinavir and 1.0-fold for ritonavir that of the exposures in humans at the recommended therapeutic dose (400/100 mg BID). There are, however, no adequate and well-controlled studies in pregnant women. KALETRA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

**Antiviral/ Pregnancy Registry:** To monitor maternal-fetal outcomes of pregnant women exposed to KALETRA, an Antiviral Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-258-4263.

**Nursing Mothers:** The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breast-feed their infants to avoid risking perinatal transmission of HIV. Studies in rats have demonstrated that lopinavir is secreted in milk. It is not known whether lopinavir is secreted in human milk. Because of both the potential for HIV transmission and the potential for serious adverse reactions in nursing infants, mothers should be instructed not to breast-feed if they are receiving KALETRA.

**Geriatric Use:** Clinical studies of KALETRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. In general, appropriate caution should be exercised in the administration and monitoring of KALETRA in elderly patients reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

**Pediatric Use:** The safety and pharmacokinetic profiles of KALETRA in pediatric patients below the age of 6 months have not been established. In HIV-infected patients age 6 months to 12 years, the adverse event profile seen during a clinical trial was similar to that for adult patients. The evaluation of the antiviral activity of KALETRA in pediatric patients in clinical trials is ongoing.

Study 940 is an ongoing open-label, multicenter trial evaluating the pharmacokinetic profile, tolerability, safety and efficacy of KALETRA oral solution containing lopinavir 80 mg/mL and ritonavir 20 mg/mL in 108 antiretroviral naive (44%) and experienced (56%) pediatric patients. All patients were non-nucleoside reverse transcriptase inhibitor naive. Patients were randomized to either 230 mg lopinavir/57.5 mg ritonavir per m<sup>2</sup> or 300 mg lopinavir/75 mg ritonavir per m<sup>2</sup>. Naive patients also received zalcitabine and stavudine. Experienced patients received nevirapine plus up to two nucleoside reverse transcriptase inhibitors.

Safety, efficacy and pharmacokinetic profiles of the two dose regimens were assessed after three weeks of therapy in each patient. After analysis of these data, all patients were continued on the 300 mg lopinavir/75 mg ritonavir per m<sup>2</sup> dose. Patients had a mean age of 5 years (range 6 months to 12 years) with 14% less than 2 years. Mean baseline CD<sub>4</sub> cell count was 638 cells/mm<sup>3</sup> and mean baseline plasma HIV-1 RNA was 4.7 log<sub>10</sub> copies/mL.

Through 48 weeks of therapy, the proportion of patients who achieved and sustained an HIV RNA < 400 copies/mL was 80% for antiretroviral naive patients and 71% for antiretroviral experienced patients. The mean increase from baseline in CD<sub>4</sub> cell count was 404 cells/mm<sup>3</sup> for antiretroviral naive and 284 cells/mm<sup>3</sup> for antiretroviral experienced patients treated through 48 weeks. At 48 weeks, two patients (2%) had prematurely discontinued the study. One antiretroviral naive patient prematurely discontinued secondary to an adverse event attributed to KALETRA, while one antiretroviral experienced patient prematurely discontinued secondary to an HIV-related event.

Dose selection for patients 6 months to 12 years of age was based on the following results. The 230/57.5 mg/m<sup>2</sup> BID regimen without nevirapine and the 300/75 mg/m<sup>2</sup> BID regimen with nevirapine provided lopinavir plasma concentrations similar to those obtained in adult patients receiving the 400/100 mg BID regimen (without nevirapine).

**ADVERSE REACTIONS: Adults: Treatment-Emergent Adverse Events:** KALETRA has been studied in 701 patients as combination therapy in Phase III and Phase III clinical trials. The most common adverse event associated with KALETRA therapy was diarrhea, which was generally of mild to moderate severity. Rates of discontinuation of randomized therapy due to adverse events were 5.8% in KALETRA-treated and 4.9% in zalcitabine-treated patients in Study 863.

Drug related clinical adverse events of moderate or severe intensity in ≥ 2% of patients treated with combination therapy for up to 48 weeks (Phase III) and for up to 72 weeks (Phase III) are presented in Table 4. For other information regarding observed or potentially serious adverse events, please see WARNINGS and PRECAUTIONS.

**Table 4: Percentage of Patients with Selected Treatment-Emergent Adverse Events of Moderate or Severe Intensity Reported in ≥ 2% of Adult Patients**

Grade	Study 863		Study 864		Study 865	
	Antiretroviral Naive (N=16)	Antiretroviral Experienced (N=14)	Antiretroviral Naive (N=16)	Antiretroviral Experienced (N=14)	Study 865 (N=16)	Study 865 (N=14)
Diarrhea	2%	2%	2%	2%	2%	2%
Headache	2%	2%	2%	2%	2%	2%
Nausea	2%	2%	2%	2%	2%	2%
Abdominal pain	2%	2%	2%	2%	2%	2%
Upper respiratory tract infection	2%	2%	2%	2%	2%	2%
Stomatitis	2%	2%	2%	2%	2%	2%
Flatulence	2%	2%	2%	2%	2%	2%
Constipation	2%	2%	2%	2%	2%	2%
Pruritus	2%	2%	2%	2%	2%	2%
Back pain	2%	2%	2%	2%	2%	2%
Arthralgia	2%	2%	2%	2%	2%	2%
Myalgia	2%	2%	2%	2%	2%	2%
Upper extremity pain	2%	2%	2%	2%	2%	2%
Lower extremity pain	2%	2%	2%	2%	2%	2%
Joint pain	2%	2%	2%	2%	2%	2%
Neck pain	2%	2%	2%	2%	2%	2%
Abdominal distention	2%	2%	2%	2%	2%	2%
Upper respiratory tract infection	2%	2%	2%	2%	2%	2%
Stomatitis	2%	2%	2%	2%	2%	2%
Flatulence	2%	2%	2%	2%	2%	2%
Constipation	2%	2%	2%	2%	2%	2%
Pruritus	2%	2%	2%	2%	2%	2%
Back pain	2%	2%	2%	2%	2%	2%
Arthralgia	2%	2%	2%	2%	2%	2%
Myalgia	2%	2%	2%	2%	2%	2%
Upper extremity pain	2%	2%	2%	2%	2%	2%
Lower extremity pain	2%	2%	2%	2%	2%	2%
Joint pain	2%	2%	2%	2%	2%	2%
Neck pain	2%	2%	2%	2%	2%	2%
Abdominal distention	2%	2%	2%	2%	2%	2%
Upper respiratory tract infection	2%	2%	2%	2%	2%	2%
Stomatitis	2%	2%	2%	2%	2%	2%
Flatulence	2%	2%	2%	2%	2%	2%
Constipation	2%	2%	2%	2%	2%	2%
Pruritus	2%	2%	2%	2%	2%	2%
Back pain	2%	2%	2%	2%	2%	2%
Arthralgia	2%	2%	2%	2%	2%	2%
Myalgia	2%	2%	2%	2%	2%	2%
Upper extremity pain	2%	2%	2%	2%	2%	2%
Lower extremity pain	2%	2%	2%	2%	2%	2%
Joint pain	2%	2%	2%	2%	2%	2%
Neck pain	2%	2%	2%	2%	2%	2%
Abdominal distention	2%	2%	2%	2%	2%	2%
Upper respiratory tract infection	2%	2%	2%	2%	2%	2%
Stomatitis	2%	2%	2%	2%	2%	2%
Flatulence	2%	2%	2%	2%	2%	2%
Constipation	2%	2%	2%	2%	2%	2%
Pruritus	2%	2%	2%	2%	2%	2%
Back pain	2%	2%	2%	2%	2%	2%
Arthralgia	2%	2%	2%	2%	2%	2%
Myalgia	2%	2%	2%	2%	2%	2%
Upper extremity pain	2%	2%	2%	2%	2%	2%
Lower extremity pain	2%	2%	2%	2%	2%	2%
Joint pain	2%	2%	2%	2%	2%	2%
Neck pain	2%	2%	2%	2%	2%	2%
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Myalgia	2%	2%	2%	2%	2%	2%
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Lower extremity pain	2%	2%	2%	2%	2%	2%
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Back pain	2%	2%	2%	2%	2%	2%
Arthralgia	2%	2%	2%	2%	2%	2%
Myalgia	2%	2%	2%	2%	2%	2%
Upper extremity pain	2%	2%	2%	2%	2%	2%
Lower extremity pain	2%	2%	2%	2%	2%	2%
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Back pain	2%	2%	2%	2%	2%	2%
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Constipation	2%	2%	2%	2%	2%	2%
Pruritus	2%	2%	2%	2%	2%	