High Prevalence of Indinavir-Associated Renal Complications in Thai HIV-Infected Patients

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Background: *Indinavir (IDV) is the protease inhibitor (PI) used most often in resource-limited countries. The present study aimed to determine the prevalence of IDV-associated renal complications as well as their clinical characteristics.*
Material and Method: *The authors reviewed all patients participating in cohorts of indinavir-containing regimens at the HIV-NAT research center during the period of indinavir treatment. Patients who had pre-existing renal diseases were excluded. Renal toxicities included presence of urologic symptoms, nephrolithiasis, abnormal urine sediments, crystalluria and loss of renal function. Radiological studies of KUB system were reviewed as well.*
Results: *Two-hundred and four patients treated with IDV were included. Median (IQR) follow up period was 216 (150-312) weeks. One hundred and eighty patients were treated with ritonavir-boosted regimens at some point, and 24 patients were treated only with unboosted regimens. Leukocyturia (51.9%) was the most common finding of IDV-associated renal complications. Thirty-five percent of patients had urologic symptoms such as flank pain or dysuria. Almost half of the patients had significant loss of renal function that was associated with prolonged use of IDV. The most common radiological finding was nephrolithiasis. Less common, but of greater clinical importance, are nephrocalcinosis or renal atrophy.*
Conclusion: *A high prevalence of IRC was found in Thai HIV-infected patients. As long as no other cost-effective boosted PI regimens are available, strategies to prevent irreversible loss of renal function are warranted.*

Keywords: *Indinavir, Nephrotoxicity, Nephrolithiasis, Nephrocalcinosis*

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Indinavir (IDV) is the most commonly used Protease Inhibitor (PI) in resource-limited countries. It is a well known cause of nephrolithiasis, interstitial nephritis, and renal insufficiency. Nephrolithiasis has been reported in 3 to 22 percent of IDV users, although a higher incidence in countries with a hot-climate is suspected[1-3]. Indinavir-associated renal toxicity is characterized by leukocyturia, often accompanied by crystalluria and interstitial nephritis, with or without urologic symptoms[4]. Importantly, irreversible loss of renal function could develop as a consequence of prolonged IDV use[5,6]. Therefore, systematic monitoring of renal complications may be required in order to avoid irreversible renal dysfunction[4].

High plasma level of IDV is among the prime risk factors of IDV-associated renal complications

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(IRC)[4]. High plasma IDV levels are frequently seen in Thai HIV-infected patients, particularly in patients with low body mass index (BMI)[7]. Concomitant administration of nephrotoxic medications such as acyclovir or co-trimoxazole increases the risk of nephrolithiasis as well[5]. Since IDV is a potent and affordable PI in Thailand, strategies to prevent its renal complications should be emphasized. Such strategies are optimizing drug exposure and monitoring patients for leukocyturia, crystalluria and loss of renal function.

To determine the prevalence and clinical characteristics of IRC in Thailand, the authors reviewed the medical records of Thai HIV-infected patients who received indinavir while participating in clinical studies for treatment of HIV infection at the HIV-NAT research center. In the present study, the authors describe a spectrum of renal manifestations including leukocyturia, crystalluria, nephrolithiasis, renal insufficiency and nephrocalcinosis.

Material and Method

The authors collected information on 220 adults (who received indinavir while participating in clinical studies for treatment of HIV infection at the HIV-NAT Netherlands Australia Thailand Research Collaboration (HIV-NAT research center) from Jan 1999 to Feb 2006. Data was extracted from patient records for the duration of time the patients were treated with IDV. Pre-existing renal diseases were excluded. The median follow-up period was 216 weeks. Indinavir was prescribed at a dosage of 1,600 mg per day with ritonavir or 2,400 mg per day without ritonavir. Serum creatinine and urinalysis were performed every 12 or 24 weeks. Ultrasonography was performed if there was a clinical indication such as rising serum creatinine, flank pain or renal colic.

Criteria of IRC

The authors defined IRC by the following criteria. (1) Crystalluria was defined by two or more of IDV crystals per high power field. (2) Leukocyturia was defined by demonstration of five or more leukocytes per high power field and the absence of urinary tract infection. (3) Nephrolithiasis was defined by either clinical criteria (acute flank pain with or without hematuria) or radiological evidence of newly formed calculi. (4) Interstitial nephritis was defined by clinical criteria (leukocyturia, proteinuria without urinary tract infection) or by renal biopsy and (5) loss of renal function was defined by increment of serum creatinine from baseline more than 0.5 mg/dl without obvious causes of renal failure.

Statistical analysis

Statistical analysis was performed by using SAS version 8.2 (Cary, NC, USA). Continuous data expressed as median and Inter-Quartile Range (IQR). Non-parametric tests were used to compare data between the two groups. Chi-square test was used to compare proportions. A p-value of less than 0.05 was considered statistically significant.

Results

A total of 220 patients received indinavir as part of HAART at HIV-NAT center during the period from January 1999 to February 2006. The authors excluded 15 patients because of incomplete data on serum creatinine and one who was lost to follow-up after the first month of IDV treatment. The final IDV users, therefore, comprised 204 patients.

Prevalence of indinavir-associated renal complications

One hundred and eight patients (53%) exhibited IRC. The median time and IQR of IDV use was 216 (150-312) weeks. Fifty-four (26%) patients began treatment with unboosted regimens, and of these, 24 (12%) remained on unboosted regimens for the duration of their treatment. One hundred and eighty (88%) patients were treated with ritonavir boosted IDV at some point. Patients began treatment with full dose regimens, and 132 (65%) patients had one or more IDV dose reductions as a consequence of toxicity. The median time to first IDV dose reduction was 144 (83-222) weeks. Table 1 shows patient demography and concomitant drug use. Univariate analysis identified duration of therapy ($p < 0.0001$), concomitant use of co-trimoxazole ($p = 0.02$), and treatment with boosted IDV regimens ($p = 0.008$) as significant factors associated with the risk of developing IRC.

The most common symptoms associated with IDV use were flank pain and renal colic (n = 52, 25%). Fourteen patients had repeated episodes of flank pain and of those, four patients had three recurrent attacks. The second most common symptom associated with IDV use was dysuria (n = 38, 19%). This was also associated with leukocyturia in 25 (66%) patients (p 0.0002) or loss of renal function in 24 (63%) patients ($p = 0.02$). Eighteen out of thirty-eight patients had combined dysuria and flank pain. Nephrolithiasis, mostly seen by ultrasonogram, occurred in 23 patients (11.3%). However, the number of patients with renal stones did not include those patients who had flank pain/renal colic

Table 1. Factors associated with loss of renal function

Characteristics	Loss of renal function*		Total n = 204	p-value
	No (n = 110)	Yes (n = 94)		
Median follow-up (IQR) Weeks	168 (72-216)	240 (216-324)	216 (150-312)	<0.0001
Median time (IQR) to loss of renal function		84 (48-120)		
Median age (IQR), year	35 (30-41)	35 (32-41)	35 (31-41)	NS
Female, number (%)	45 (41)	30 (32)	75 (37)	NS
Weight < 60 kg, number (%)	69 (63)	53 (56)	122 (60)	NS
BMI < 22, number (%)	62 (56)	50 (53)	112 (55)	NS
Route of HIV infection, n (%)				
Homosexual	10 (9)	10 (11)	20 (10)	NS
Heterosexual	86 (78)	80 (85)	166 (81)	
Other/unknown	14 (13)	4 (4)	18 (9)	
CDC stage, n (%)				
A or B	89 (81)	73 (78)	162 (79)	NS
C	20 (18)	21 (22)	41 (20)	
Co-trimoxazole use, n (%)				
No	59 (54)	35 (37)	94 (46)	0.02
Yes	51 (46)	59 (63)	110 (54)	
Urologic symptoms, n (%)				
No	88 (80)	45 (48)	133 (65)	<0.0001
Yes	22 (20)	49 (52)	71 (35)	
Leukocyturia, n (%)				
No	91 (83)	33 (35)	124 (61)	<0.0001
Yes	19 (17)	61 (64)	80 (39)	
Ritonavir boosted IDV at anytime, n (%)				
No	19 (17)	5 (5)	24 (12)	0.008
Yes	91 (83)	89 (95)	180 (88)	

* Serum creatinine > 0.5mg/dl above baseline
** IQR: inter-quartile range

without abnormal radiological imaging (n = 45).

Loss of renal function was the most common laboratory finding (46.1%) (Table 2). Although patients who did not have any loss of renal function had a shorter follow-up than those who experienced renal dysfunction, the median time to development of renal dysfunction was approximately half of the median duration of follow-up in those who did not develop renal toxicity. Patients who developed loss of renal function were more likely to have a history of urologic symptoms ($p < 0.0001$) and leukocyturia ($p < 0.0001$). The significant association of loss of renal function with leukocyturia was present whether the patients had urologic symptoms ($p = 0.001$) or not ($p < 0.0001$).

Radiological findings of indinavir-associated renal complications (Table 3)

Seventy-two patients required a radiological study mostly by ultrasonography. The most common

Table 2. Clinical characteristics and frequency of indinavir-associated renal complications

	Total cases (n = 204)	Frequency (%)
Crystalluria	38	18.6
Nephrolithiasis	23	11.3
- by radiological evidence	20	9.8
- passing stone	4**	2.0
Leukocyturia	80	39.2
Hematuria	31	15.2
Urologic symptoms	71	34.8
- dysuria	38***	18.6
- flank pain/renal colic	52	25.5
- frequency	2	1.0
Loss of renal function*	94	46.1

* rising of serum creatinine > 0.5 mg/dl
** 2 patients had passed a stone without radiological evidence of nephrolithiasis
*** 10 patients had combined symptoms with flank pain or renal colic

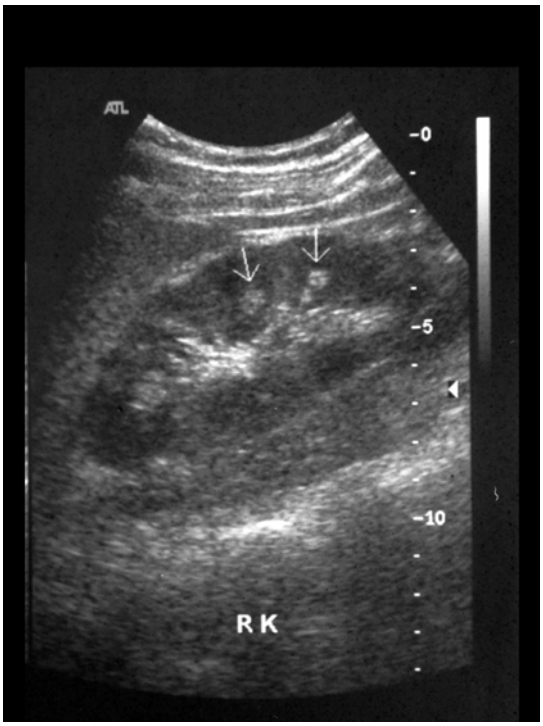

Fig. 1 Ultrasonogram shows two renal calculi (arrows)

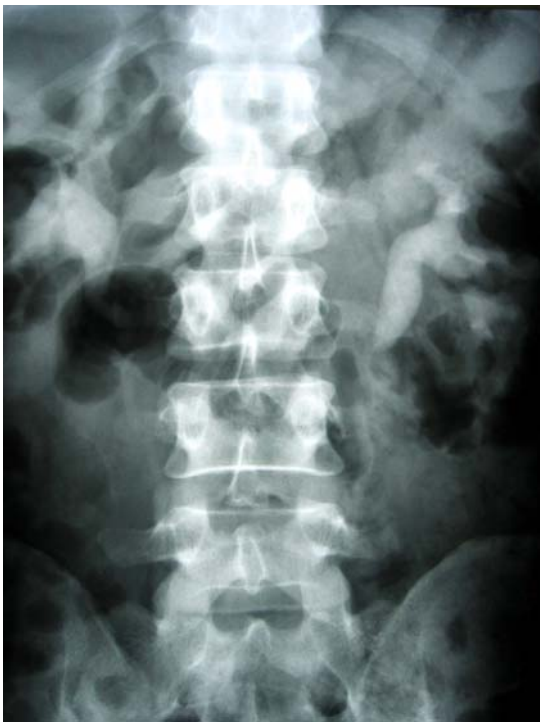

Fig. 2 Intravenous pyelogram shows bilateral ureteric obstruction

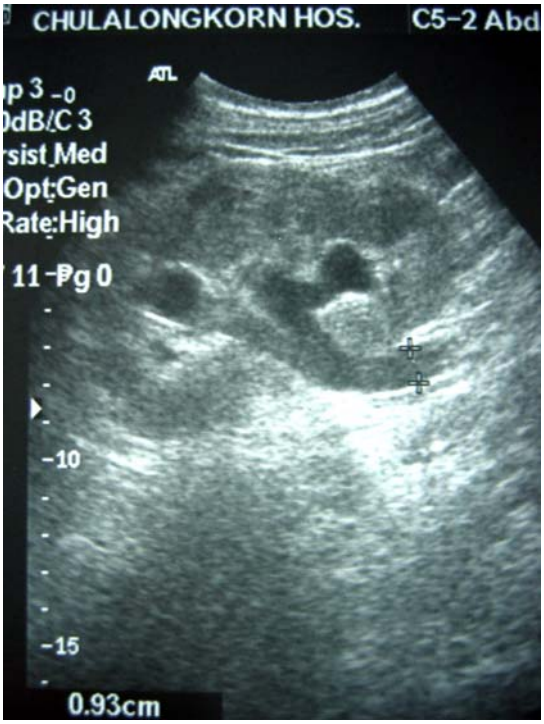

Fig. 3 Ultrasonogram shows hydroureter and hydronephrosis

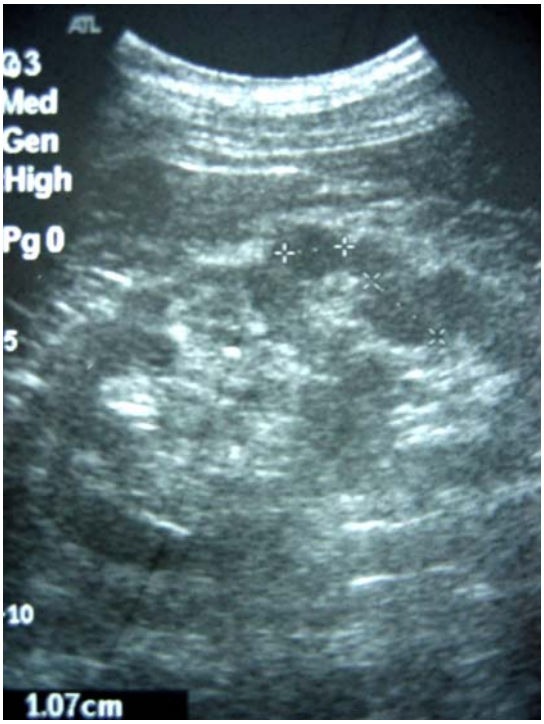

Fig. 4 Ultrasonogram shows nephrocalcinosis

Table 3. Radiological findings of indinavir-associated renal complications

Findings	n = 72	Percent
Nephrolithiasis	20	27.8
Increased parenchymal echo	18	25
Nephrocalcinosis	12	16.7
Decreased kidney size	10	13.9
Pelvocalyceal dilatation	10	13.9
Cortical lobulation	9	12.5
Cortical thinning	9	12.5
Hydronephrosis	8	11.1
Enlarged kidney	2	2.7
Focal hyperechoic lesion at upper pole of right kidney	1	1.4

indication for performing the present study was renal dysfunction and urologic symptoms. Nephrolithiasis was the most common finding and was present in 23 cases (Fig. 1). Less common, but a clinical important finding, was decreased kidney size. Other radiological findings included obstructive uropathy (hydronephrosis (Fig. 2, 3) pelvocalyceal dilatation, enlarged kidney) and nephrocalcinosis (Fig. 4).

Discussion

In this long-term cohort of Thai HIV-infected patients, the incidence of IRC was unexpectedly high. Almost 50% of patients had a clinically significant loss of renal function. Although many patients had urological symptoms related to IDV use, a significant proportion of patients had renal dysfunction without any warning symptoms. A significant proportion of those who developed renal dysfunction also had a history of leukocyturia. Of interest, this association of leukocyturia with loss of renal function occurred whether or not the patient experienced urologic symptoms. This association of leukocyturia with loss of renal function is consistent with the findings of Dieleman et al[4] who reported repeated occurrences of leukocyturia as a prelude to the loss of renal function. Therefore, since leukocyturia may be an earlier sign of IDV associated nephrotoxicity performing routine urinary examination and measurement of renal function in HIV-infected patients who use IDV-containing therapy are warranted.

The incidence of IRC was previously reported in 8 to 22 percent of patients[1,2,5]. Nephrolithiasis was the most common presentation among IRC. In the present study, the incidence of nephrolithiasis as defined by radiological evidence was 11.3 percent. This number may be an under-estimate since there were a large number of patients who had flank pain without radiological changes. Therefore, it is presumed that the incidence of nephrolithiasis in the present study may be up to 30 percent and would be in agreement with the report of Martinez et al[3] of up to 50% of patients in a country with a hot climate.

In the present study, nephrocalcinosis was found in 16.7 percent of radiological findings. All patients had renal dysfunction associated with IDV use. Nephrocalcinosis represents a form of intra-renal calcification that is occasionally reported in IRC[5]. This might be related to crystallization in the renal parenchyma with subsequent deterioration in renal function[8]. It is not known whether nephrocalcinosis could be reversible after IDV withdrawal. In the present study, IDV was switched to another PI in one patient, and 2 years later nephrocalcinosis was resolved but the serum creatinine remained abnormal.

Loss of renal function occurred in 46.1% of patients in the present report and was the highest number compared to other studies (Table 4). Since this cohort is the longest follow-up period in IDV user, it is likely that the incidence of renal dysfunction is directly associated with the duration of IDV exposure. In the present study concomitant use of co-trimoxazole increased risk of renal dysfunction, a factor that may be of concern in those patients with CD4 counts less than 200 cells/mm^3 who require prophylaxis against Pneumo-

Table 4. Comparison of IRC among different reports

	This study	Kopp et al[1]	Dieleman et al[4,10]
Median follow-up time (week)	216	30	48
Crystalluria	18.6%	20%	45%
Nephrolithiasis	11.3%	3-8%	8.3%
Leukocyturia	39.2%	n/a	35%
Presence of urologic symptoms	34.8%	8%	10%
Loss of renal function	46.1%	n/a	26%

cystis pneumonia. At present, the pathophysiologic mechanisms underlying the declining renal function is not known, but it might involve occult interstitial nephritis as well as asymptomatic tubular obstruction by indinavir crystals[4,8,9].

Low lean BMI and peak plasma IDV levels (Cmax) are among the most important risk factors of IRC[10]. During the study period, the patients who participated in studies at HIV-NAT center had relatively high peak plasma levels[7]. Recently, dose reduction protocol or IDV switching have already implemented and it is believed that rate of IRC could be reduced thereafter[11]. Recently, the authors suggested a lower dose IDV protocol such as indinavir/ritonavir 400/100 BID combination with 2 nucleoside reverse transcriptase inhibitors (NRTI) since good efficacy and lower side-effects were reported[12-14].

Of the five currently approved protease inhibitors in Thailand, IDV has been the most widely used because of the relatively low cost, its efficacy, its favorable pharmacologic properties, its low pill burden and its inclusion in regimens endorsed by the National Access Program for HIV & AIDS (NAPHA). It currently remains the most affordable PI in resource-limited countries. The efforts in Thailand to bring the cost of other more tolerable PIs to a more affordable level are underway. Nonetheless, it is important that physicians who treat HIV-infected patients with IDV be aware of the possible spectrum of urologic complications. Systematic monitoring of renal complications should be implemented to facilitate early diagnosis and treatment of these reversible complications.

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อุบัติการณ์ของภาวะแทรกซ้อนทางไตจากยาอินดินาเวียร์

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วัตถุประสงค์: *อินดินาเวียร์เป็นยาต้านไวรัสในกลุ่มโปรติเอส อินฮิบิเตอร์ ที่มีการใช้กันมากในกลุ่มประเทศที่กำลังพัฒนา การศึกษานี้มีจุดมุ่งหมายเพื่อหาความชุกของภาวะแทรกซ้อนทางไตจากยาอินดินาเวียร์ในผู้ป่วยชาวไทยที่ติดเชื้อเอดส์*

วัสดุและวิธีการ: *ได้ทำการศึกษาอาการแทรกซ้อนทางไตจากเวชระเบียนและการตรวจทางรังสีวิทยาของผู้ป่วยติดเชื้อเอดส์ที่ได้รับยาอินดินาเวียร์จากโครงการวิจัยทางคลินิกของศูนย์วิจัยโรคเอดส์ สภากาชาดไทย กลุ่มอาการแทรกซ้อนทางไตที่เกิดจากยาอินดินาเวียร์ได้แก่ ปวดหลัง ปัสสาวะขัด นิ่วในทางเดินปัสสาวะ พบเซลล์เม็ดเลือด หรือ ผลึกของยาจากการตรวจปัสสาวะ หรือ การทำงานของไตบกพร่อง*

ผลการศึกษา: *ในผู้ป่วยจำนวน 204 รายที่ได้รับยาอินดินาเวียร์เป็นระยะเวลาเฉลี่ย 216 สัปดาห์ มีการตรวจพบเม็ดเลือดขาวในปัสสาวะสูงที่สุดถึงร้อยละ 51.9 พบอาการปวดหลังหรือปัสสาวะขัดได้ร้อยละ 35 และประมาณครึ่งหนึ่งของผู้ป่วยที่มีการทำงานของไตบกพร่อง ส่วนการตรวจทางรังสีวิทยาพบนิ่วในทางเดินปัสสาวะได้มากที่สุด รองลงมาได้แก่ภาวะเนโฟรแคลซิโนซิส หรือไตหดเล็กลง*

สรุป: *พบภาวะแทรกซ้อนทางไตจากยาอินดินาเวียร์ในผู้ป่วยติดเชื้อเอดส์ชาวไทยที่ความชุกสูง แพทย์ควรหาแนวทางร่วมกันในการป้องกันการทำงานของไตบกพร่องที่มีสาเหตุจากยานี้*