Indinavir: the forgotten HIV-protease inhibitor. Does it still have a role?

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Indinavir is one of four first-generation HIV-protease inhibitors and was the most popular amongst them in the late 1990s. It was initially licensed for use alone, given three times daily, administered away from meals and together with at least 1.5 litres of fluid per day. In clinical practice, it became common for clinicians to prescribe it with a ritonavir pharmacokinetic 'boost' to remove the food restriction, reduce the pill burden and enable a more convenient twice-daily dosing schedule. However, at a ritonavir-boosted dosing schedule of indinavir/ritonavir 800/100 mg b.i.d., the regimen proved toxic and poorly tolerable, and its use diminished as newer, better tolerated PIs became available. Recent research has suggested that ritonavir-boosted indinavir administered at lower doses, particularly indinavir/ritonavir 400/100 mg b.i.d., retains potency and is considerably less toxic. As a result, there is interest in its application in resource-constrained settings.

1. Introduction

The year 2006 marked 25 years since the first cases of AIDS were recognised. It also marked the 10-year anniversary of the introduction of combination antiretroviral therapy (cART) in the management of HIV infection. The era of cART commenced in 1996, a year in which a number of key findings and breakthroughs regarding the nature and management of HIV infection were made, and their various implications crystallised around the International AIDS Conference held that year in Vancouver, British Columbia, Canada. The first key insight was that during the chronic phase of infection (defined as the 'latent period' between acute infection and the development of AIDS), rather than becoming quiescent, HIV continues to replicate at exceedingly high rates [1]. Complementary to this discovery was the advent of technology that gave us the capacity to quantify the HIV load using new molecular techniques, such as the polymerase chain reaction (PCR) [2]. In Vancouver, John Mellors presented population data that demonstrated a correlation between the HIV load and the rate of $CD4^+$ cell decline [3]. Finally, 1996 was the year in which data were first presented regarding the potency of HIV-protease inhibitors and non-nucleoside reverse transcriptase inhibitors, particularly when used in combination with nucleoside reverse transcriptase inhibitors [4,5]. In 1997, two major studies describing the use of indinavir as a component of cART were published back to back in the same edition of *The New England Journal of Medicine* [4,6] and, at that time, and for a few years thereafter, indinavir became the dominant PI on the market.

This review examines and describes the history of the development and the application of indinavir to the treatment of HIV infection in adults and adolescents as part of cART, including its use as single PI therapy and in ritonavir-boosted form. The paper also evaluates recent research that suggests that, when used at a reduced dose and boosted with ritonavir, indinavir retains potency, but demonstrates

improved safety and tolerability. As a result, indinavir may be a useful PI for continued use, particularly in resource-limited settings where access to PIs is limited.

2. Introduction to the compound

Indinavir sulfate is a hydroxyaminopentane amide and a potent and specific inhibitor of the HIV protease. It was identified from a series of PIs developed in the 1990s using rational drug design techniques. The structure of indinavir is shown in **Figure 1**.

2.1 Pharmacology

Indinavir is a competitive inhibitor of the HIV protease, binding to the active site of the enzyme [7]. It has seven active metabolites, one glucuronide conjugate and six oxidative metabolites [8]; however, these metabolites contribute little to its activity. Indinavir is 60% protein bound in humans. The CYP450 enzyme complex is the major source of its metabolism, in particular the CYP3A4 subset. Indinavir is rapidly absorbed in a fasted state, with a T_{max} of 30 – 60 min. At the approved dose of 800 mg every 8 h, the mean (s.d.) AUC is 30,601 ± 11,401 nM•h (n = 16), with a mean (s.d.) C_{max} and C_{trough} of 12,617 ± 4037 (n = 16) and 251 ± 178 nM (n = 16), respectively. Indinavir exhibits substantial inter- and intra-patient variability, particularly when administered in the unboosted three times daily form. Absorption of indinavir is reduced by up to 80% if administered with a meal high in calories, fat and protein; lighter meals cause little or no change in AUC, C_{max} or C_{trough} levels.

3. Clinical development

3.1 Phase I/II clinical trials

In a Phase I/II trial, 22 patients with p24 antigenemia were administered indinavir [9]. After 400 mg every 6 h for 12 days, serum p24 values decreased by 70%, and the median CD4+ cell increase was 77 cells/mm³. In a second trial of four patients dosed at 600 mg every 6 h, serum RNA levels declined by 1 – 3 logs in all four patients. However, after 16 weeks, viral load had returned to baseline in all participants, and two subjects exhibited decreased sensitivity to indinavir *in vitro*. In a study of 70 HIV-infected patients with CD4+ cell counts of 150 – 500 cells/mm³ and serum RNA > 20,000 copies/ml, escalating doses of indinavir were given. The drug was generally well tolerated and the dose of 800 mg every 8 h was selected for further evaluation [10].

3.2 Pivotal Phase III clinical trials

In a large, randomised, controlled, clinical end-point study, 1156 patients not previously treated with lamivudine or PIs were stratified according to CD4+ cell count (≤ 50 versus 51 – 200 cells/mm³) and randomly assigned to one of two daily regimens: zidovudine 600 mg (or stavudine) and lamivudine 300 mg, or the regimen with indinavir 800 mg

t.i.d. The primary end point was the time to the development of the AIDS or death. The proportion of patients whose disease progressed to AIDS or death was lower with indinavir, zidovudine and lamivudine (6%) than with zidovudine and lamivudine alone (11%; estimated HR = 0.50; 95% CI = 0.33 – 0.76; p = 0.001). Mortality in the two groups was 1.4% and 3.1 percent, respectively (estimated HR 0.43; 95% CI = 0.19 – 0.99; p = 0.04). The effects of treatment were similar in both CD4+ cell strata. The responses of CD4+ cells and plasma HIV-1 RNA paralleled the clinical results. The authors concluded that treatment with indinavir, zidovudine and lamivudine (compared with zidovudine and lamivudine alone) significantly slowed the progression of HIV-1 disease in patients with ≤ 200 CD4+ cells/mm³ and prior exposure to zidovudine [6].

In a separate trial in zidovudine-experienced patients, indinavir in combination with zidovudine and lamivudine was compared with indinavir alone or the dual nucleoside reverse transcriptase inhibitor combination of zidovudine/lamivudine [4]. In this double-blind study, 97 HIV-infected patients who had received zidovudine treatment for at least 6 months, had 50 – 400 CD4+ cells/mm³ and at least 20,000 copies of HIV RNA per µl were randomly assigned to one of three treatments for up to 52 weeks: indinavir 800 mg every 8 h; zidovudine 200 mg every 8 h combined with lamivudine 150 mg b.i.d.; or all three drugs. The patients were followed to monitor the occurrence of adverse events, changes in viral load and CD4+ cell counts. The decrease in HIV RNA over the first 24 weeks was greater in the three-drug group than in the other groups (p < 0.001 for each comparison). RNA levels decreased to < 500 copies/µl at week 24 in 28 of 31 patients in the three-drug group (90%), 12 of 28 patients in the indinavir group (43%) and none of 30 patients in the zidovudine-lamivudine group. The increase in CD4+ cell counts over the first 24 weeks was greater in the two groups receiving indinavir than in the zidovudine-lamivudine group (p ≤ 0.01 for each comparison). The changes in the viral load and the CD4+ cell count persisted for up to 52 weeks. All of the regimens were generally well tolerated. The incidence of unconjugated hyperbilirubinaemia was greater in the indinavir-containing arms.

4. Early postmarketing studies

4.1 Studies of ritonavir-boosted indinavir with nucleoside backbone

A number of indinavir studies have been reported since its licensing in the late 1990s. One of these studies is the only clinical outcome study conducted to directly compare the use of a PI with its ritonavir-boosted alternative. The study examined indinavir in its licensed 800 mg t.i.d. schedule with a ritonavir-boosted regimen of indinavir/ritonavir 800/100 mg b.i.d., both given in combination with zidovudine/lamivudine in NRTI-experienced patients (excluding lamivudine exposure) [11]. The study reported 112 weeks of
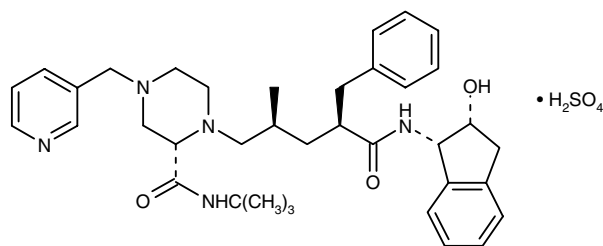
Figure 1. Chemical structure of indinavir sulfate

follow up and demonstrated comparable efficacy (on an intention-to-treat analysis 64 and 60% of patients had an HIV RNA < 50 copies/ml of therapy after 112 weeks of therapy in the twice- and three-times-daily regimens, respectively [p = 0.7]), but at the cost of marginally greater toxicity and intolerability in the ritonavir-boosted twice-daily arm. The long-term (272 week) follow up of this study suggested that although indinavir-containing regimens are potent, they are often toxic, but also suggested that this may be improved by indinavir dose reduction [12].

During the period in which ritonavir boosting of HIV PIs was gaining favour as a strategy, Merck & Co. Inc. funded a study that enrolled 343 patients receiving an indinavir 800 mg t.i.d regimen with $CD4^+$ > 100 cells/µl and HIV RNA < 500 copies/ml for ≥ 3 months, and randomised them to either continue indinavir three times daily dosing or to switch to indinavir/ritonavir 800/100 mg b.i.d. without change in other antiretrovirals. Over a 48-week period, they demonstrated equivalence of the three-times-daily dosing versus switching to twice-daily ritonavir-boosting, but also found that the boosted strategy in this patient population was associated with greater intolerability. In retrospect, the strategy was somewhat flawed in that by selecting a population who had been demonstrably able to tolerate indinavir given three times daily in the short-term, they inevitably demonstrated apparently greater intolerability when these patients switched to a regimen associated with an altered indinavir pharmacokinetic profile [13].

A randomised trial that compared indinavir/ritonavir 800/100 mg b.i.d. head to head with ritonavir-boosted saquinavir 1000/100 mg b.i.d. with background nucleoside reverse transcriptase inhibitor therapy, found comparable antiretroviral effects between the two regimens, with no difference in the time to virological failure, but a greater number of treatment-limiting adverse events in the indinavir-containing arm [14].

The pharmacodynamics associated with the use of indinavir in its 800 mg t.i.d. and ritonavir-boosted twice daily regimens have been reported [15]. This substudy of the HIV-NAT 005 study [11] demonstrated AUC break points for nephrotoxicity of 30 and 60 mg•h/l and C_{min} break points for virological failure of 0.1 mg/l and 0.25 mg/l in the three-times- and twice-daily arms, respectively. A group of French investigators has independently reported that an indinavir C_{trough} > 0.5 mg/l is likely to be associated with toxicity [16].

4.2 Studies of indinavir combined with non-nucleoside reverse transcriptase inhibitors

In the pivotal, randomised, open-label Merck 006 study, 450 patients who had not previously been treated with lamivudine, a non-nucleoside reverse-transcriptase inhibitor or a PI were randomly assigned to one of three regimens: efavirenz (600 mg/day) plus zidovudine (300 mg b.i.d.) and lamivudine (150 mg b.i.d.); indinavir (800 mg every 8 h) plus zidovudine and lamivudine; or efavirenz plus indinavir (1000 mg every 8 h). In the intention to treat analysis, the efavirenz and indinavir arm performed better than the indinavir and zidovudine/lamivudine arm, with 53 and 48% of patients with HIV RNA levels of < 400 copies/ml after 48 weeks, respectively [17].

Indinavir/ritonavir 800/100 mg b.i.d. given in combination with efavirenz 600 mg/day has also been studied in combination as an NRTI-sparing regimen in 61 patients with substantial prior exposure to combination NRTI therapy [18]. After 96 weeks, 69% of patients had an HIV RNA level of < 50 copies/ml in an intention-to-treat analysis. In recently reported 4-year follow up of this cohort, 75% of patients maintained an HIV RNA level of < 50 copies/ml on the originally assigned regimen (intention-to-treat analysis). A substantial proportion of patients (42 of 49 on the original regimen [86%]) had undergone an indinavir dose reduction using therapeutic drug monitoring guidance, and none of those who had undergone indinavir dose reduction had subsequently lost virological control [19]. This study also reported the pharmacokinetics for both active antiretroviral agents in the regimen. Despite the known pharmacokinetic interaction between efavirenz and indinavir, adequate minimum concentrations of both drugs were demonstrated [20].

5. Indinavir-associated toxicities

Indinavir is associated with specific adverse effects as well as general adverse effects associated with PIs as a class (see **Table 1**). The mechanism by which indinavir causes the specific toxicities of hyperbilirubinaemia, nephrolithiasis and chronic renal impairment have been investigated and reported. Zucker *et al.* found that the characteristic elevations in serum unconjugated bilirubin associated with indinavir therapy were associated with direct inhibition of bilirubin-conjugating activity occurring as a result of competitive inhibition of UDP-glucuronosyltransferase (UGT) [21]. As predicted, it has been shown that those displaying particular polymorphisms in the *UGT1A1* gene are more likely to demonstrate hyperbilirubinaemia in the presence of indinavir [21,22].

The pathogenesis of indinavir-associated nephrolithiasis and renal impairment has been more difficult to determine. However, a reasonable body of evidence supports the notion that indinavir directly causes nephrolithiasis and renal impairment as a result of crystallisation in the urinary tract and a resultant inflammatory response [23-25]. A recent report has suggested that even in the setting of chronic renal

Table 1. Adverse effects of HIV-protease inhibitors.

Protease inhibitor	Specific adverse effects	Probable protease-inhibitor class effects
Indinavir	Clinical nephrolithiasis Chronic renal impairment Hyperbilirubinaemia Cutaneous toxicities (e.g., nail dystrophy, dry skin)	Gastrointestinal disturbance Metabolic disturbance Body-fat distribution abnormalities Hepatotoxicity Paraesthesias Hypersensitivity reactions
Saquinavir	–	As above
Ritonavir	–	As above
Nelfinavir	–	As above
Ritonavir-boosted lopinavir	–	As above
Fosamprenavir	–	As above
Atazanavir	Hyperbilirubinaemia	As above
Tipranavir	Intracranial haemorrhage	As above
Darunavir	–	As above

impairment associated with medium term exposure to indinavir-containing therapy, there is the potential for continuation of the drug using therapeutic drug monitoring to optimise the dose, and that if this is achieved, there may be an improvement in renal function, although not necessarily back to pre-indinavir exposure baseline levels [26]. Studies have suggested that co-factors such as administration of concomitant co-trimoxazole [24] as well as baseline anthropometry [24,27] may increase the risk of indinavir-associated nephrolithiasis. Another study suggested that ambient environmental temperature is a risk-factor for indinavir-associated nephrolithiasis [28]. This is of particular concern for the use of indinavir in resource-poor settings, many of which are located in the tropics.

6. Studies of lower doses of indinavir with ritonavir-boosting

As a result of toxicity and intolerability of indinavir, as well as evidence that its combination with low-dose ritonavir could improve the pharmacokinetic profile of indinavir and allow for twice-daily doing [29], recent clinical studies have examined the potential for the use of lower doses of indinavir given twice daily in a ritonavir-boosted form. In general, the evidence suggests that the use of indinavir/ritonavir at doses as low as 400/100 mg b.i.d. is associated with maintained potency and minimal toxicity in populations in both developed- and developing-world settings [30-39]. In 2003, two French studies were published that formally examined the use of reduced doses of indinavir in ritonavir-boosted form in patients successfully treated with combination therapy containing a standard indinavir 800 mg t.i.d regimen [30], and in antiretroviral-naive patients [31]. In the study in which patients switched from indinavir 800 mg t.i.d to indinavir/ritonavir 400/100 mg b.i.d., all 20 enrolled patients

continued with plasma levels of HIV RNA levels of < 200 copies/ml and tolerability of the regimen was excellent [30]. In the naive study, after 48 weeks, 65% of patients had plasma HIV RNA level of < 400 copies/ml by intention-to-treat analysis [31]. Pharmacokinetics drawn from patients in the study of Ghosn *et al.* (800 mg t.i.d reduced to indinavir/ritonavir 400/100 mg b.i.d. in patients with plasma HIV RNA levels of < 200 copies/ml) demonstrated more favourable pharmacokinetics for the b.i.d. regimen (increased indinavir C_{min} [0.48 mg/l b.i.d. versus 0.2 mg/l t.i.d at week 4] and reduced indinavir C_{max} [3.0 mg/l b.i.d. versus 8.5 mg/l t.i.d at week 4]). As noted above, pharmacokinetic–pharmacodynamic relationships for indinavir have been described [15,16]. Subsequent studies of ritonavir-boosted indinavir have supported these observations. In particular, a study of the use of indinavir/ritonavir 400/100 mg b.i.d. in a cohort of 80 clinically advanced (median CD4+ count 16 cells/mm³, median baseline HIV RNA 174,000 copies/ml) HIV-infected, antiretroviral-naive patients resulted in 69% of patients returning a plasma HIV RNA level of < 50 copies/ml after 96 weeks of treatment, amongst the best results ever described for a boosted-PI containing regimen. In a pharmacokinetic substudy performed within a random sample of this prospective cohort, the pharmacokinetic profiles were comparable to those observed in France (see **Table 2**) [37].

A number of other studies have also suggested that indinavir/ritonavir 400/100 mg b.i.d. is a potent and effective boosted PI combination [34,38,39]. However, there have been no randomised, controlled trials to determine the relative performance of one ritonavir-boosted dose of indinavir against another, nor have there been randomised, controlled trials of reduced dose, ritonavir-boosted indinavir against other boosted-PIs as either first- or second-line therapy. Therefore, it is not possible to state which boosted-PI (and at what dose combination) is best on a head-to-head comparative basis,

Table 2. Pharmacokinetic parameters of indinavir (at doses of either 800 or 400mg) alone or in combination with ritonavir (100mg) in HIV-infected adults.

Study	Indinavir (mg)	Ritonavir (mg)	Number of patients	Dosing schedule	C_{min} (mg/l)	C_{max} (mg/l)
Crixivan® Product monograph [42]	800	0	16	t.i.d.	0.25	12.62
*Burger et al. [15]	800	0	19	t.i.d.	0.13	8.1
van Heeswijk et al. [43]	800	100	6	b.i.d.	0.99	8.7
Arnaiz et al. [13]	800	100	10	b.i.d.	0.50	10.0
*Burger et al. [15]	800	100	17	b.i.d.	0.68	10.6
Ghosn et al. [30]	400	100	20	b.i.d.	0.38	3.9
‡Boyd et al. [37]	400	100	19	b.i.d.	0.17	4.1
‡Cressey et al. [38]	400	100	13	b.i.d.	0.17	3.8

C_{max}: Maximum concentration of drug; C_{min}: Minimum concentration of drug.

Most studies were conducted in separate cohorts in different countries with distinct baseline characteristics.

*These two data sets were derived from a randomised trial of indinavir 800 t.i.d. versus indinavir/ritonavir 800/100mg b.i.d., conducted in Thailand.

‡These two data sets were derived from two seperate cohort studies in Thailand.

and there is an urgent need for properly powered, international, multi-centre, randomised, controlled trials to help determine the optimal boosted-PI, particularly for use in resource-limited settings.

7. Resistance to indinavir

As a result of its error-prone replication, HIV generates many mutants, a small proportion of which are replication competent and may naturally confer resistance to particular antiretroviral agents. Resistance to the PIs, including indinavir, is generally associated with amino acid changes in the active site or in neighbouring regions involved in inhibitor binding. For ritonavir-boosted indinavir, mutations in the HIV-1 Gag cleavage sites at codons 10, 20, 24, 32, 36, 46, 54, 71, 73, 77, 82, 84 and 90 are associated with resistance; mutations at position 82 and 84 are strongly associated with treatment failure with indinavir [40].

8. Patented and generic indinavir and drug cost

The patent for indinavir (Crixivan®) was issued to Merck & Co. in the USA in 1995. Generic versions of indinavir are produced by a number of pharmaceutical manufacturers in India as well as one manufacturer in Argentina. The Argentinean product, Inhibisam® (Richmond Laboratories), was found to provide a similar exposure to indinavir in a crossover pharmacokinetic study of 10 patients [41]. None of these products has received WHO prequalification.

If one uses the quoted first-category price for indinavir listed in the Medecins Sans Frontieres (MSF) 'Untangling the web'

document (the price for which buyers in the UN designated 'least developed' countries are eligible), the cost per person per year for the indinavir component alone (administered at 400 mg b.i.d.) would be US$200 per person per year (i.e., ~ 50 US cents/day). If one adds the cost of two 100-mg doses of ritonavir to this (at the MSF quoted cost from the originator company of US$83 per person per year), the total cost of the ritonavir-boosted combination is US$283 per person per year, < US$1 per day. This is 57% of the cost of the cheapest version of ritonavir-boosted lopinavir, and thereby represents by far the cheapest boosted-PI option in the developing world at the time of writing [101].

9. Expert opinion and conclusions

In the developed world, indinavir is essentially a forgotten drug. In the most recent revision of the USA Department of Health and Human Services (DHHS) guidelines it does not make an appearance in the list of recommended PIs [102]. However, the use of indinavir at lower doses, and in particular the use of indinavir/ritonavir 400/100 mg b.i.d., has the potential to provide reasonably affordable access to a boosted-PI in developing countries where cost is a major barrier to antiretroviral treatment. Present WHO guidelines for the use of antiretroviral therapy in developing countries recommends the inclusion of a boosted-PI in second-line antiretroviral therapy; the guidelines do not differentiate between boosted indinavir, fosamprenavir, saquinavir, lopinavir or atazanavir, although they do mention that indinavir is a less attractive alternative because of the associated nephrolithiasis. This caveat would appear to be based on the data accumulated on the administration of boosted indinavir at

800/100 mg b.i.d. As a result of the poor experience of MSF with the use of boosted-indinavir-containing therapy (at indinavir/ritonavir 800/100 mg b.i.d.) in their antiretroviral access programmes in developing countries, indinavir was dropped from the mid-2006 antiretroviral pricing guide. However, on the basis of the evidence regarding ritonavir-boosted reduced dose indinavir, it has been reincluded in a revision to the document at the end of 2006 [101].

Therefore, the long and often difficult clinical experience with the use of indinavir has led us to a point at which it may, in fact, provide a desperately needed answer to the problem of finding a compact, safe and affordable PI regimen for use in developing countries. Given that widespread access to NNRTI-based combination antiretroviral regimens in developing countries is now entering its fifth year, the time is now right for the conduct of rigorous, international studies of ritonavir-boosted reduced-dose indinavir as a key component of a regimen for patients failing first-line therapy. In this way, we may, in the near future, be able to offer an effective second-line regimen to HIV-infected patients in the developing world.

Bibliography

1. PERELSON AS, NEUMANN AU, MARKOWITZ M, LEONARD JM, HO DD: HIV-1 dynamics *in vivo*: virion clearance rate, infected cell life-span, and viral generation time. *Science* (1996) **271**(5255):1582-1586.

2. MARSCHNER IC, COLLIER AC, COOMBS RW *et al.*: Use of changes in plasma levels of human immunodeficiency virus Type 1 RNA to assess the clinical benefit of antiretroviral therapy. *J. Infect. Dis.* (1998) **177**(1):40-47.

3. MELLORS JW, MUNOZ A, GIORGI JV *et al.*: Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann. Intern. Med.* (1997) **126**(12):946-954.

4. GULICK RM, MELLORS JW, HAVLIR D *et al.*: Treatment with indinavir, zidovudine, and lamivudine in adults with human immunodeficiency virus infection and prior antiretroviral therapy. *N. Engl. J. Med.* (1997) **337**(11):734-739.

5. MONTANER JS, REISS P, COOPER D *et al.*: A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. Italy, The Netherlands, Canada and Australia Study. *JAMA* (1998) **279**(12):930-937.

6. HAMMER SM, SQUIRES KE, HUGHES MD *et al.*: A controlled trial of two nucleoside analogues plus indinavir in persons with human immunodeficiency virus infection and CD4 cell counts of 200 per cubic millimeter or less. AIDS Clinical Trials Group 320 Study Team. *N. Engl. J. Med.* (1997) **337**(11):725-733.

7. DORSEY BD, LEVIN RB, MCDANIEL SL *et al.*: L-735,524: the design of a potent and orally bioavailable HIV protease inhibitor. *J. Med. Chem.* (1994) **37**(21):3443-3451.

8. BALANI SK, ARISON BH, MATHAI L *et al.*: Metabolites of L-735,524, a potent HIV-1 protease inhibitor, in human urine. *Drug Metab. Dispos.* (1995) **23**(2):266-270.

9. DEUTSCH P, TEPPLER H, SQUIRES K *et al.*: Antiviral activity of L-735,524, an HIV protease inhibitor in infected patients. *Program and abstracts of the 34th Interscience Conference on Antimicrobial Agents and Chemotherapy*. Orlando, USA (1994) Abstract I59.

10. STEIGBEL RT, BERRY P, MELLORS J, MAHON D: Efficacy and safety of the HIV protease inhibitor indinavir sulfate (MK 639) at escalating dose. *Program and abstracts of the 4th International Conference on Retroviruses and Opportunistic Infections*. Washington, DC, USA (22 – 26 January 1996). Abstract 146.

11. BOYD MA, SRASUEBKUL P, KHONGPHATTANAYOTHIN M *et al.*: Boosted versus unboosted indinavir with zidovudine and lamivudine in nucleoside pre-treated patients: a randomized, open-label trial with 112 weeks of follow-up (HIV-NAT 005). *Antivir. Ther.* (2006) **11**(2):223-232.

12. AVIHINGSANON A, KERR SJ, BOYD MA *et al.*: Long–term efficacy, safety, and tolerability of indinavir-based therapy in nucleoside experienced HIV-1-infected patients in a resource limited setting: 272 week follow-up of the HIV-NAT 005 study. *Program and abstracts of the XVI International AIDS Conference*. Toronto, Canada (13 – 18 August 2006). Abstract no. WEPE0121.

13. ARNAIZ JA, MALLOLAS J, PODZAMCZER D *et al.*: Continued indinavir versus switching to indinavir/ritonavir in HIV-infected patients with suppressed viral load. *AIDS* (2003) **17**(6):831-840.

14. DRAGSTED UB, GERSTOFT J, PEDERSEN C *et al.*: Randomized trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human immunodeficiency virus Type 1-infected patients: the MaxCmin1 Trial. *J. Infect. Dis.* (2003) **188**(5):635-642.

15. BURGER D, BOYD M, DUNCOMBE C *et al.*: Pharmacokinetics and pharmacodynamics of indinavir with or without low-dose ritonavir in HIV-infected Thai patients. *J. Antimicrob. Chemother.* (2003) **51**(5):1231-1238.

16. SOLAS C, BASSO S, POIZOT-MARTIN I *et al.*: High indinavir Cmin is associated with higher toxicity in patients on indinavir-ritonavir 800/100 mg twice-daily regimen. *J. Acquir. Immune Defic. Syndr.* (2002) **29**(4):374-377.

17. STASZEWSKI S, MORALES-RAMIREZ J, TASHIMA KT *et al.*: Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N. Engl. J. Med.* (1999) **341**(25):1865-1873.

18. BOYD MA, SIANGPHOE U, RUXRUNGTHAM K *et al.*: Indinavir/ritonavir 800/100 mg bid and efavirenz 600 mg qd in patients failing treatment with combination nucleoside reverse transcriptase inhibitors: 96-week outcomes of HIV-NAT 009. *HIV Med.* (2005) **6**(6):410-420.

19. AVIHINGSANON A, BOYD MA, PORNPRASIT P *et al.*: Long term durability of boosted indinavir and efavirenz in patients with combination nucleoside failure in a resource constrained setting:

4-year follow-up of HIV-NAT 009. *Program and abstracts of the XVI International AIDS Conference.* Toronto, Canada (13 – 18 August 2006). Poster THPE0126.

20. BOYD MA, AARNOUTSE RE, RUXRUNGTHAM K *et al.*: Pharmacokinetics of indinavir/ritonavir (800/100 mg) in combination with efavirenz (600 mg) in HIV-1-infected subjects. *J. Acquir. Immune Defic. Syndr.* (2003) **34**(2):134-139.

21. ZUCKER SD, QIN X, ROUSTER SD *et al.*: Mechanism of indinavir-induced hyperbilirubinemia. *Proc. Natl Acad. Sci. USA* (2001) **98**(22):12671-12676.

22. BOYD MA, SRASUEBKUL P, RUXRUNGTHAM K *et al.*: Relationship between hyperbilirubinaemia and UDP-glucuronosyltransferase 1A1 (UGT1A1) polymorphism in adult HIV-infected Thai patients treated with indinavir. *Pharmacogenet. Genomics* (2006) **16**(5):321-329.

23. KOPP JB, MILLER KD, MICAN JA *et al.*: Crystalluria and urinary tract abnormalities associated with indinavir. *Ann. Intern. Med.* (1997) **127**(2):119-125.

24. BOUBAKER K, SUDRE P, BALLY F *et al.*: Changes in renal function associated with indinavir. *AIDS* (1998) **12**(18):F249-F254.

25. DIELEMAN JP, GYSSENS IC, VAN DER ENDE ME, DE MARIE S, BURGER DM: Urological complaints in relation to indinavir plasma concentrations in HIV-infected patients. *AIDS* (1999) **13**(4):473-478.

26. BOYD MA, SIANGPHOE U, RUXRUNGTHAM K *et al.*: The use of pharmacokinetically guided indinavir dose reductions in the management of indinavir-associated renal toxicity. *J. Antimicrob. Chemother.* (2006) **57**(6):1161-1167.

27. MERAVIGLIA P, ANGELI E, DEL SORBO F *et al.*: Risk factors for indinavir-related renal colic in HIV patients: predictive value of indinavir dose/body mass index. *AIDS* (2002) **16**(15):2089-2093.

28. MARTINEZ E, LEGUIZAMON M, MALLOLAS J, MIRO JM, GATELL JM: Influence of environmental temperature on incidence of indinavir-related nephrolithiasis. *Clin. Infect. Dis.* (1999) **29**(2):422-425.

29. HSU A, GRANNEMAN GR, CAO G *et al.*: Pharmacokinetic interaction between ritonavir and indinavir in healthy volunteers. *Antimicrob. Agents Chemother.* (1998) **42**(11):2784-2791.

30. GHOSN J, LAMOTTE C, AIT-MOHAND H *et al.*: Efficacy of a twice-daily antiretroviral regimen containing 100 mg ritonavir/400 mg indinavir in HIV-infected patients. *AIDS* (2003) **17**(2):209-214.

31. DUVIVIER C, MYRTO A, MARCELIN AG *et al.*: Efficacy and safety of ritonavir/indinavir 100/400 mg twice daily in combination with two nucleoside analogues in antiretroviral treatment-naive HIV-infected individuals. *Antivir. Ther.* (2003) **8**(6):603-609.

32. WASMUTH JC, LA PORTE CJ, SCHNEIDER K, BURGER DM, ROCKSTROH JK: Comparison of two reduced-dose regimens of indinavir (600 mg versus 400 mg twice daily) and ritonavir (100 mg twice daily) in healthy volunteers (COREDIR). *Antivir. Ther.* (2004) **9**(2):213-220.

33. LEE LS, PANCHALINGAM A, YAP MC, PATON NI: Pharmacokinetics of indinavir at 800, 600, and 400 milligrams administered with ritonavir at 100 milligrams and efavirenz in ethnic chinese patients infected with human immunodeficiency virus. *Antimicrob. Agents Chemother.* (2004) **48**(11):4476-4478.

34. KONOPNICKI D, DE WIT S, POLL B, CROMMENTUYN K, HUITEMA A, CLUMECK N: Indinavir/ritonavir-based therapy in HIV-1-infected antiretroviral therapy-naive patients: comparison of 800/100 mg and 400/100 mg twice daily. *HIV Med.* (2005) **6**(1):1-6.

35. RHAME FS, RAWLINS SL, PETRUSCHKE RA *et al.*: Pharmacokinetics of indinavir and ritonavir administered at 667 and 100 milligrams, respectively, every 12 hours compared with indinavir administered at 800 milligrams every 8 hours in human immunodeficiency virus-infected patients. *Antimicrob. Agents Chemother.* (2004) **48**(11):4200-4208.

36. MOOTSIKAPUN P, CHETCHOTISAKD P, ANUNNATSIRI S, BOONYAPRAWIT P: Efficacy and safety of indinavir/ritonavir 400/100 mg twice daily plus two nucleoside analogues in treatment-naive HIV-1-infected patients with CD4+ T-cell counts < 200 cells/mm3: 96-week outcomes. *Antivir. Ther.* (2005) **10**(8):911-916.

37. BOYD M, MOOTSIKAPUN P, BURGER D *et al.*: Pharmacokinetics of reduced-dose indinavir/ritonavir 400/100 mg twice daily in HIV-1-infected Thai patients. *Antivir. Ther.* (2005) **10**(2):301-307.

38. CRESSEY TR, LEENASIRIMAKUL P, JOURDAIN G *et al.*: Low-doses of indinavir boosted with ritonavir in HIV-infected Thai patients: pharmacokinetics, efficacy and tolerability. *J. Antimicrob. Chemother.* (2005) **55**(6):1041-1044.

39. JUSTESEN US, LEVRING AM, THOMSEN A, LINDBERG JA, PEDERSEN C, TAURIS P: Low-dose indinavir in combination with low-dose ritonavir: steady-state pharmacokinetics and long-term clinical outcome follow-up. *HIV Med.* (2003) **4**(3):250-254.

40. JOHNSON VA, BRUN-VEZINET F, CLOTET B, KURITZKES D, PILLAY D, SCHAPIRO JM, RICHMAN DD: Update of the drug resistance mutations in HIV-1: Fall 2006. *Topics in HIV Medicine* (2006) **14**:125-130.

41. ZALA C, ALEXANDER CS, OCHOA C *et al.*: Comparable pharmacokinetics of generic indinavir (Inhibisam) versus brand indinavir (Crixivan) when boosted with ritonavir. *J. Acquir. Immune Defic. Syndr.* (2005) **38**(3):363-364.

42. MERCK & CO., INC.: Crixivan® (indinavir sulfate) capsules prescribing information. Merck & Co., Inc. Rahway (NJ) USA (1996).

43. VAN HEESWIJK RP, VELDKAMP AI, HOETELMANS RM *et al.*: The steady-state plasma pharmacokinetics of indinavir alone and in combination with a low dose of ritonavir in twice daily dosing regimens in HIV-1-infected individuals. *AIDS* (1999) **13**(14):F95-F99.

Websites

101. http://www.accessmed-msf.org/documents/untanglingtheweb%209.pdf
Medicines Sans Frontieres: Campaign for Access to Essential Medicines. Untangling the web of price reductions: a pricing guide for the purchase of ARVs for developing countries. 9th Edition, July 2006 (revised). Accessed 23 March 2007.

102. http://aidsinfo.nih.gov/ContentFiles/Adultan
dAdolescentGL.pdf
US Department of Health and Human
Services: Guidelines for the Use of
Antiretroviral Agents in HIV-1-Infected
Adults and Adolescents – October 10,
2006. Accessed 23 March 2007.

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