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

Mark Boyd
National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, 376 Victoria Street, Darlinghurst 2010, NSW, Australia

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.

Keywords: HIV, indinavir, resource-limited setting, ritonavir boosted-protease inhibitor

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 hydroxymatinopentane 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 nMh (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...
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 PI's 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 tolerability. 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 sub-study of the HIV-NAT 005 study [11] demonstrated AUC break points for nephrotoxicity of 30 and 60 mg*h/l and Cmin 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 Cough > 0.5 mg/l is likely to be associated with toxicity [16].
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 dosing [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 $C_{\text{min}}$ [0.48 mg/l b.i.d. versus 0.2 mg/l t.i.d at week 4] and reduced indinavir $C_{\text{max}}$ [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/mm 3, 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 sub-study 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 1. Adverse effects of HIV-protease inhibitors.

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

---

**Indinavir**

**Table 1. Adverse effects of HIV-protease inhibitors.**

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

---

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Indinavir (mg)</th>
<th>Ritonavir (mg)</th>
<th>Number of patients</th>
<th>Dosing schedule</th>
<th>C_min (mg/l)</th>
<th>C_max (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crixivan® Product</strong></td>
<td>800</td>
<td>0</td>
<td>16</td>
<td>t.i.d.</td>
<td>0.25</td>
<td>12.62</td>
</tr>
<tr>
<td>*Burger et al. [15]</td>
<td>800</td>
<td>0</td>
<td>19</td>
<td>t.i.d.</td>
<td>0.13</td>
<td>8.1</td>
</tr>
<tr>
<td>*van Heeswijk et al. [43]</td>
<td>800</td>
<td>100</td>
<td>6</td>
<td>b.i.d.</td>
<td>0.99</td>
<td>8.7</td>
</tr>
<tr>
<td>Arnaiz et al. [13]</td>
<td>800</td>
<td>100</td>
<td>10</td>
<td>b.i.d.</td>
<td>0.50</td>
<td>10.0</td>
</tr>
<tr>
<td>*Burger et al. [15]</td>
<td>800</td>
<td>100</td>
<td>17</td>
<td>b.i.d.</td>
<td>0.68</td>
<td>10.6</td>
</tr>
<tr>
<td>Ghosn et al. [30]</td>
<td>400</td>
<td>100</td>
<td>20</td>
<td>b.i.d.</td>
<td>0.38</td>
<td>3.9</td>
</tr>
<tr>
<td>Boyd et al. [37]</td>
<td>400</td>
<td>100</td>
<td>13</td>
<td>b.i.d.</td>
<td>0.17</td>
<td>4.1</td>
</tr>
<tr>
<td>Cressey et al. [38]</td>
<td>400</td>
<td>100</td>
<td>13</td>
<td>b.i.d.</td>
<td>0.17</td>
<td>3.8</td>
</tr>
</tbody>
</table>

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 separate cohort studies in Thailand.
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


43. SCHAPIRO JM, RICHMAN DD: 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.


Indinavir


Affiliation
Mark Boyd BA, MHID, MD, FRACP
National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, 376 Victoria Street, Darlinghurst 2010, NSW, Australia
Tel: + 61 2 9385 0900; Fax: + 61 2 9385 0920;
E-mail: mboyd@nchecr.unsw.edu.au
Senior Lecturer, Therapeutic and Vaccine Research Program, National Centre in HIV Epidemiology and Clinical Research, University of New South Wales, 376 Victoria Street, Darlinghurst 2010, NSW, Australia