New HIV protease inhibitors for drug-resistant viruses

Stefano Rusconi† & Ottavia Viganò
†Author for correspondence
Cattedra di Malattie Infettive e Tropicali, Dipartimento di Scienze Cliniche "Luigi Sacco", Università degli Studi, via G.B. Grassi 74, 20157 Milano, Italy
Tel.: +39 023 904 3350 Fax: +39-025 031 9758 stefano.rusconi@unimi.it

Keywords: clinical efficacy, drug-resistance, HIV-1, novel compounds, protease inhibitors, response

Several second-generation protease inhibitors have been developed over the last few years. These compounds have been used in preregistrative clinical trials or are currently in various Phases (I, II or III) of their progress towards use in HIV-1-infected patients. All drugs in this category have been designed in order to reach high plasma levels and possibly overcome the issue of cross-resistance among the compounds belonging to this class. Taking into account the rapid occurrence of protease inhibitor cross-resistance, clinicians who are treating patients living with HIV/AIDS will need new active protease inhibitors in the near future. These newly developed compounds will be the subject of our review.

An overview of antiretroviral therapy
An impressive acceleration has been observed regarding drug discovery activity towards the anti-HIV-1 agents over the last decade. Nucleoside and non-nucleoside inhibitors of reverse transcriptase (RT) have demonstrated high antiviral activity both in vitro and in vivo [1–3]. However, RT inhibitors have shown only transient efficacy when administered as single or dual therapy because of the emergence of resistant viral variants [4–7]. On the basis of the evidence that viral protease is essential to the life cycle of HIV-1, and after the development of first-generation HIV-1 protease inhibitors (PIs) [8–12], the introduction of PIs into combination-therapy regimens has resulted in a marked improvement in clinical outcomes [13–16].

Combination regimens aim to suppress viral replication in infected individuals for as long as possible. Nevertheless, residual viral activity often persists during therapy and this condition represents an ideal requisite for the emergence of drug-resistant viral variants with low susceptibility to all classes of HIV-1-inhibitory compounds [17–19]. This indicates that the selection of resistant viral mutants is driven by drug pressure [20,21], and may also be sustained by a reduced adherence to antiretroviral regimens and suboptimal levels of anti-HIV compounds in bodily fluids. Within the PI class of compounds, HIV-1 variants resistant to one compound have shown different degrees of cross-resistance to other PIs currently available [22–27]. In this context, combination therapy against HIV-1 requires not only the monitoring of CD4+ lymphocytes and viral load, but also the introduction of genotypic resistance tests and drug-sensitivity assays in order to guide treatment decisions for HIV-1-infected patients [28,29]. Taking all these issues into consideration, the management of HIV/AIDS infection has become much more complicated than before, and discrepancies between treated and untreated populations have become wider and wider.

Medical needs
The pandemic phenomenon determined by HIV/AIDS spread in such a rapid fashion as to cause a disaster in terms of global health – the tragic burden was especially apparent in low-resourced countries [30]. According to the 2004 United Nations (UN) AIDS data, at the end of 2004 39.4 million people were living with HIV/AIDS, 3.1 million died and 4.9 million were newly infected during 2004. Among those who had been infected in 2004, 95% were from poor countries and of these, approximately 70% live in sub-Saharan Africa [101].

Drug availability through highly active antiretroviral therapy (HAART) – a combination of at least three drugs with or without a fusion inhibitor – has dramatically changed the history of the infection as well as the related morbidity and mortality [31,32]. HIV/AIDS has become, at least in developed countries, a manageable disease, also allowing for novel approaches such as structured treatment interruptions (STIs).

There is absolute need for novel antiretroviral agents. Of course, improvement of adherence and appropriate selection of first-line regimens are crucial factors determining the future development of resistance to antiretrovirals. It is evident from the HIV/AIDS pandemic that improvements in current agents are needed, in
terms of greater antiretroviral potency, activity towards drug-resistant viruses, fewer adverse events and availability of reaching tissue and cellular reservoirs. An increasing number of patients are failing multiple PI-including regimens, which would imply the failure of all three classes of anti-HIV drugs in many circumstances. These patients need new therapeutic options, either new uses of regimens with existing drugs, new agents with unique resistance profiles or different mechanisms of suppressing the virus.

Activity of protease inhibitors

The HIV protease is responsible for cleavage of the gag and gag-pol precursor polyproteins to the structural and functional proteins, granting the maturation and infectivity of progeny viruses. HIV PIs exert their activity during the late stages of viral replication, thus interfering with the formation of functionally active virions. Given this indubitable activity, new regimens, including PIs, present new challenges, such as an amelioration of patient compliance (through a simple and practical schedule), an attempt to overcome adverse events, such as the occurrence of lipodystrophy, and an introduction of more bioavailable compounds. This would likely include novel dual PI-boosted regimens and provide a more efficient method of attaining sustained viral suppression in naïve or chronically treated HIV-1-infected individuals. Several pharmaceutical companies have developed, or are in the process of developing, an increasing number of second-generation PIs, either with or without a flexible structure and peptidomimetic, over the last few years. These novel compounds will be reviewed herein.

Resistance to protease inhibitors

In 1988, the protease enzyme of HIV-1 was crystallized and its 3D structure determined [33], allowing for the rapid development of PIs. Initially, it was hypothesized that HIV-1 protease, unlike RT, would be unable to accommodate mutations, thus leading to drug resistance had obviously been unproven. PIs have significantly changed the prognosis of HIV-1 infection. However, their use is associated with the appearance of a large pattern of single mutations in the protease gene inhibitors which favors the development of multidrug resistance (MDR) to other compounds within the same class of drugs [34,35]. Condra and colleagues gave the first virologic demonstration of cross-resistance to PIs in patients subjected to indinavir (IDV) monotherapy [23]. Together with the progressive accumulation of mutations selected by IDV monotherapy, these patients harbored viruses that also became resistant to other PIs such as saquinavir (SQV) and amprenavir (APV) [22]. The follow-up of this study demonstrated that the extent of IDV resistance and cross-resistance to other PIs depended upon the single amino acid substitutions, their number and the combination in which they appeared [23]. Ritonavir (RTV) has also been described as potentially inducing a large extent of unique or cross-resistance within the PI class [36]. Resistance to PIs occurs as a result of amino acid substitutions inside the substrate-binding domain of the protease or at distant sites, so-called compensatory mutations [22,37,38]. These amino acid changes reduce affinity between the PI and the protease [39], such as in the V82A mutation [40]. The complex picture of emergence of cross-resistance to PIs was reported in several studies performed both in vitro [41,42] and in vivo [26,38,43]. Additional data are becoming available on PI-related resistance following sequential treatment with several compounds within this class of drugs. Winters and colleagues have recently reported that an initial treatment with SQV may cause a full development of cross-resistance to IDV and nelfinavir (NFV) in patients that will receive such regimens as part of an active anti-HIV-1 combination therapy [24]. Duloustit and colleagues have observed that previous therapy with SQV followed by IDV allowed for a viral evolution that maintained the initial selection of drug resistance and adapted the viral population to IDV pressure [25]. These results suggest that HIV-1 quasispecies would likely be able to adapt to the presently available drugs, which target the same enzyme. Taking into account the rapid occurrence of PI cross-resistance, clinicians treating HIV-1-infected patients will need improved, active PIs in the near future.

Compounds

Tipranavir

Tipranavir (TPV) (Figure 1) is a nonpeptidomimetic inhibitor of the HIV protease [44] and demonstrates little cross-resistance with the other PIs. Previous papers demonstrated the efficacy of TPV against a wide spectrum of drug resistant isolates [45]. TPV demonstrated elevated dose-response properties against a variety of isolates derived from HIV-1-infected subjects with multidrug resistance to other PIs [46]. After these
proof-of-principle papers, TPV was selected for development for clinical use in HIV-1-infected patients. Further evidences indicated that TPV was optimally effective when used with a boosting dose of RTV coadministered at a dose of 200 mg twice a day.

TPV received accelerated approval by the US Food and Drug Administration (FDA) in June 2005, and later by the European Agency for the Evaluation of Medicinal Products (EMEA). Data supporting this process comes from two Phase III trials, Randomized Evaluation of Strategic Intervention in multidrug reSistant patients with Tipranavir (RESIST) 1 and 2. Patients enrolled in the these studies complied with the following requirements:

- Were failing their current PI-based regimen
- Had received at least two previous PI-based regimens
- Had received prior treatment from at least three classes of antiretroviral agents
- Had documented PI resistance

These trials examined the treatment response at 24 weeks of TPV/RTV versus a comparator group in which patients received one of several marketed RTV-boosted PIs. Comparator PIs chosen using the resistance test included lopinavir (LPV), IDV, SQV and APV. Patients in both groups received an optimized background regimen of other antiretrovirals. The median baseline viral load and CD4+ counts were 4.82 log_{10} copies/ml and 155 cells/µl, respectively. A significantly greater proportion of patients receiving regimens that contain TPV/RTV were able to reduce their HIV–RNA to below 50 copies/ml than in the comparator group. At 24 weeks, 34% of patients in the TPV/RTV group and 16% of patients in the comparator group achieved a viral load of less than 400 copies/ml, and 23 versus 9% achieved less than 50 copies/ml. Patients treated with TPV/RTV presented higher CD4 values than those treated with a RTV-boosted comparator PI. The median change from baseline in the CD4+ cell count at week 24 was +34 cells/µl in patients receiving TPV/RTV (n = 582) versus +4 cells/µl in the comparator group (n = 577).

Using information from these trials, the investigators were able to build a TPV mutation score in order to predict future responses to the compound. The TPV mutation score includes 21 mutations at 16 amino acid loci identified as: 10V, 13V, 20M/R/V, 33F, 35G, 36I, 43T, 46L, 47V, 54A/M/V, 58E, 69K, 74P, 82L/T, 83D, and 84V [74]. At week 24, the virologic response based on the TPV mutation score was demonstrated as -2.1, -1.4, -0.6, -0.5, -0.4 and -0.7 log_{10} copies/ml for one, two, three, four, five and either greater than or equal to six mutations included in the TPV mutation score, respectively. In general, TPV/RTV-based therapies were superior to the comparator group regardless of total baseline protease mutations, number of primary PI mutations and number of protease-resistance-associated mutations (PRAMs) [47,48].

An anticipated toxicity of this compound involves the liver, thus a careful monitoring of liver function tests is recommended in patients treated with TPV.

**TMC 114 (Tibotec BVBA)**

TMC 114 (UIC-94017) (Figure 2) is a nonpeptidic PI currently in Phase III trials. This drug is another promising candidate for treating HIV-1-infected individuals harboring MDR viruses. The compound is a structural analog of TMC 126 (UIC-94003) developed by Tibotec BVBA, formerly Tibotec-Virco NV. TMC 126 showed activity against MDR viral isolates at extremely small concentrations and atypical mutation patterns when resistance does emerge. TMC 126 was able to block in vitro viral replication at femtomolar concentrations against a broad spectrum of multidrug resistant isolates of HIV-1 retaining high potency and less specificity. The compound inhibited wild-type and PI-resistant clinical isolates of HIV-1 at subfemtomolar concentrations with inhibitory concentrations at 50% (IC50) from 0.0003 to 0.0005 µM against a wide spectrum of HIV-1 isolates [49]. TMC-126 was also active...
against multi-PI-resistant strains derived from patients who did not respond to multiple antiretroviral treatments. \textit{In vitro} passage with TMC-126 was selected for a novel mutation, A28S, in the active region of the protease \cite{49}. A single comparative study showed that drug-resistant viruses appeared more slowly for TMC-126 than other PIs in current use. The TMC-126-resistant strains presented different genetic pathways \cite{50}.

Similar to TMC-126, TMC-114 has an excellent activity profile against HIV-1 isolates that are highly resistant to current PIs. The compound was designed after taking into consideration the structural modification induced in the protease by other PIs. TMC-114 is chemically related to APV, and differs from the latter compound by a \textit{bis}-tetrahydrofuran (THF) moiety \cite{51}. This \textit{bis}-THF moiety causes additional interactions with the Asp29 position within the protease and improving its antiviral activity \cite{51}. The compound was further investigated for its anti-HIV-1 activity \textit{in vitro}. Ghosh and colleagues first demonstrated the antiviral activity of UIC-PI in H9-infected cells \cite{52}. Koh and colleagues evidenced a potent activity (IC50 \textasciitilde 0.003 \(\mu\)M and IC90 \textasciitilde 0.009 \(\mu\)M) against multi-PI-resistant HIV isolates \textit{in vitro} and also against HIV-1 isolates selected for resistance to SQV, IDV, NFV or RTV (IC50 0.003–0.029 \(\mu\)M), although it was less active against variants selected for resistance to APV (IC50 0.22 \(\mu\)M) \cite{53}. A recent paper further stressed the strong activity of TMC 114, its EC50 was in the micromolar range against a panel of HIV strains resistant to current PIs, defined as having a fold increase in EC50 greater than or equal to 10 for at least one of the inhibitors: in addition TMC114 was very potent against multi-PI-resistant HIV, with EC50s below (or around) 10 nM against the panel strains. Its fold increase in EC50 was less than or equal to 4 against a panel of HIV strains resistant to current PIs, defined as having a fold increase in EC50 greater than or equal to 10 for at least one of the tested PIs \cite{54}.

Data related to two Phase II randomized clinical trials were presented in pretreated HIV-1-positive patients during the 12th Conference on Retroviruses and Opportunistic Infections (CROI) in Boston (MA, USA) in February 2005 \cite{55}. The compound has been selected for use at a dose of 600 mg twice a day, pharmacologically boosted with RTV 100 mg twice a day. This dosage schedule led to the antiviral effect of decreasing HIV–RNA by the order of 1.85 \log_{10} after 24 weeks of treatment. TMC/RTV demonstrated a wide efficacy in three class-experienced subjects with limited treatment options. TMC/RTV was safe and generally well tolerated. The mean CD4 cell change was +75 \(\mu\)l versus +15 \(\mu\)l in the PI comparator group. More recently, results from a 14-day proof-of-principle Phase IIA trial were reported (the TMC-114-C207 Study) \cite{56}. Results from this trial indicated a significant decrease in HIV–RNA, with a median of 1.38 \log_{10} copies/ml, when TMC-114 was used as a replacement for PIs in a nonsuppressive antiretroviral regimen over a 14-day period. The compound was safe and well tolerated by the enrolled subjects. TMC-114 is expected to come to market during 2006.

\textit{BILA-2185 BS (Boehringer Ingelheim, Inc.)} One of the most promising members of palinavir analogs is BILA-2185 BS (Figure 3) which showed high antiviral activity in inhibiting HIV-1 replication \textit{in vitro}. Beginning with palinavir, Boehringer Ingelheim described a series of new compounds in which the P3–2 quinaldic–valine portion of palinavir was replaced by 2,6-dimethylyphenoxyacetyl. BILA-2185 BS showed an IC50 value of 1.6 nM and an EC50 of 2 nM, and exhibited a favorable pharmacokinetic profile, with a 61\% apparent oral bioavailability in rats \cite{57}. However, the compound caused significant reductions in heart rates and blood pressure in animal toxicology studies which prevented further development. HIV-1 variants showing a high-level resistance (up to 1,500-fold) to the substrate analog PIs BILA-1906 BS and BILA-2185 BS were characterized \cite{58}. Active-site mutations V32I and I84V/A were consistently
In vitro studies with recombinant mutant proteases demonstrated that these mutations resulted in up to 10^4-fold increases in the K_i values toward BILA-1906 BS and BILA-2185 BS and a concomitant 2200-fold decrease in catalytic efficiency of the enzymes towards a synthetic substrate. When introduced into viral molecular clones, protease mutations impaired polyprotein processing, consistent with a decrease in enzyme activity in virions. Despite these observations, however, most mutations had little effect on viral replication except when the active-site mutations V32I and I84V/A were coexpressed in the protease. The latter combinations not only conferred a significant growth reduction of viral clones on peripheral blood mononuclear cells, but also caused the complete disappearance of mutated clones when cocultured with the wild-type virus on T-cell lines. Furthermore, the double nucleotide mutation, I84A, rapidly reverted to I84V upon drug removal, confirming its impact on viral fitness.

**DMP 450 (Bristol Myers Squibb Co.)**

DMP 450 (Mozenavir) (Figure 4) is a nonpeptidic cyclic urea HIV-1 PI currently in clinical development in Phase I/II trials to evaluate the antiviral efficacy, pharmacokinetics and toxicity. It is an inhibitor of cytochrome P450 3A4 (CYP3A4), the isoenzyme responsible for the metabolism of the peptidomimetic PI [59]. A preclinical study of pharmacokinetic DMP 450 showed a dose-dependent inhibition of HIV-1 replication of 99.9% at 0.5 µM. DMP 450 is toxic in some animals when used at high concentrations.

DMP 450 is being used in ongoing clinical studies. A Phase I/II dose-escalation trial (DMP 102) has been conducted in antiviral-naive patients randomized to receive DMP 450 or IDV in combination with d4T (stavudine) and 3TC (lamivudine). The majority of patients experienced viral-load suppression (<400 cp/ml) at 24 weeks. The compound was demonstrated to be well tolerated with no toxicity [60]. Moreover, DMP 450 showed less metabolic effects over IDV. In fact, the compound had less effects on lipidic and glucose metabolism when administered for 28 days in healthy volunteers [61]. In order to identify variants resistant to DMP 450, HIV-1 viruses were passaged in the presence of increasing concentrations of the cyclic urea inhibitor. Resistant variants contain five mutations in the protease gene: K45I, M46L, V82I, I84V and L90M, as well as an increase in IC90 levels [62]. The key residues associated with resistance between the five mentioned are Val 82 and Ile 84. The K_i value of the I84V mutant increases 25-fold compared with wild-type strains, the value for V82F decreases by two-fold and that of the mutant with the two combined substitutions by 1000-fold. Effects of these changes are not additive. Cross-resistance between cyclic urea inhibitors such as DMP 450 with DMP 323, was evidenced. This compound is no longer in development.

**PL100 (Procyon Biopharma, Inc.)**

PL100 is a novel PI currently in preclinical evaluation (Figure 5). The compound belongs to a series of PIs based on an L-lysine scaffold [63]. The selected compound, PL100, showed an interesting
resistance profile when tested against drug-resistant isolates. PL100 had a favourable cross-resistance profile when compared with marketed PIs such as SQV, IDV, NFV, APV, atazanavir (ATV) and LPV. In antiviral tests using MT4 cells, the compound had a median-fold change (FC) 4.5-fold lower than the other PIs. Linear regression between PL100 and the approved PIs evidenced a weak correlation with APV ($r^2 = 0.51$) and LPV ($r^2 = 0.49$) [64]. A PL100 back-up analog, PL337, has been recently reported at the XIV International Drug Resistance Workshop in Quebec City (Canada) in June 2005, and showed a very strong activity against MDR viruses with an EC50 of 0.014 to 0.05µM and a FC of 0.4 to 1.5. PL100 and its phosphorilated prodrug PPL100 demonstrated an excellent pharmacokinetic profile: at 100 mg/kg PPL100, boosted with RTV, maintained above 630 ng/ml for 6 h allowing a concentration greater than a protein-binding adjusted EC90 against the majority of tested strains with three to four mutations [65]. This class of compounds is expected to start Phase I clinical trials in the first half of 2006.

**AG-001859 (Pfizer, Inc.)**

AG-001859 (Figure 6) is a novel PI in the preclinical phase of development that demonstrates potent *in vitro* antiviral activity against strains of HIV resistant to the currently approved PIs. AG-001859 belongs to a series of novel allophenylnorstatin-containing PIs. AG-001859 is a tight binding inhibitor of both wild-type and 184V/L90M HIV protease with a $K_i$ of less than 0.1 nM against both enzymes. The compound exhibited an antiviral activity against wild-type HIV with an EC50 of 14 to 60 nM and MDR HIV isolates with a median EC50 of 34 nM (ranging from 5.3–420 nM). There was no correlation between the antiviral activity of AG-001859 and the number of PI-resistance mutations [66]. The ability of HIV to develop *in vitro* resistance to AG-001859 was evaluated by serial passage of wild-type HIV-1 NL4–3 in the presence of increasing concentrations of the compound. Strains of HIV-1 resistant to AG-001859 were slow to emerge, with a gradual increase in AG-001859 resistance observed as mutations in the protease and gag cleavage sites accumulated [67].

**GW640385 (GlaxoSmithKline, Inc.)**

GW640385 is a novel PI in Phase I/II of clinical development (Figure 7). GW640385 was shown to be more potent than LPV, APV, NFV, and IDV against a panel of PI-resistant clinical isolates with an average of eight protease mutations. *In vitro* IC50s ranged from 0.1 to 14.9 nM against these isolates, 80% of which had an IC50 at or below 0.8 nM [68]. The low oral bioavailability of GW640385 was corrected by the administration of low dose RTV as booster; plasma GW640385 exposure increased ~30-fold following a single dose of RTV 100mg [69].

Resistance and *in vitro* selection have been reported in recent years. The phenotypic and genotypic resistance was defined as the appearance of dual protease mutations I54L/M+I84V and a mean fold change increase greater than 3 in the phenotypic resistance, compared with sensitive isolates [70]. High *in vitro* pressure of wild-type HIV-1 with GW640385 has been carried out leading to the selection of the novel A28S mutation in the protease region which was associated with a significant loss of phenotypic susceptibility [71].
A double-blind, randomized, placebo-controlled, repeat-dose, escalating study was conducted in six sequential cohorts of healthy subjects (n = 10/cohort, eight active/two placebo). Study doses were administered for 15 days. Plasma 640385 concentrations were measured using a validated liquid chromatography–tandem mass spectrometry (LC/MS/MS) assay. Repeat administration of 640385 (±RTV) was safe and well tolerated without serious or Grade 3/4 adverse events. Mild-to-moderate adverse events potentially related to 640385 or 640385/RTV included headache, fatigue, lightheadedness, nausea, diarrhea, abdominal discomfort, rash and pruritis. All 640385/RTV twice-daily regimens achieved median day-15 640385 C above 28 ng/ml, the estimated clinical target based on in vitro IC50 for PI-resistant virus adjusted for protein binding [72].

Resistant-Repellent™ Drugs
Sequoia Pharmaceuticals synthesized a series of compounds defined as resistant repellent (RR). These compounds interact with a conserved substructure of the protease active site that is relatively unaffected by mutations known to cause drug resistance. This is a series of five compounds (SPI-70095 has a molecular weight of 656). The average IC50 for wild-type virus is 7 nM and for MDR viruses is 15 nM. The CC50 is greater than 25 µM. These compounds possess a high selectivity index (>1000). There is currently no information on pK data. The series of RR compounds is entering Phase I clinical trials [73]. At the end of 2005, no additional information is available.

Expert commentary
PIs play a pivotal role in combination therapy against HIV-1, thus it is mandatory to exploit strategies using better compounds directed against this enzyme, taking into consideration the problem of cross-resistance. The drugs presented herein have shown very interesting chemical characteristics and resistance patterns. Serious attempts to explore the feasibility of drug therapeutics with these compounds are ongoing. Clinical trials of the newest among these drugs are always preceded by clarifying pharmacokinetic issues in healthy volunteers. Many among these PIs are, or will be in the near future, involved in Phase III head-to-head randomized clinical trials with PIs currently considered the ideal comparison in optimized antiretroviral regimens.

Outlook
New compounds within the class of PIs are strongly needed to improve treatment efficacy, reduce toxicity, and provide wider therapeutic options for patients who failed multiple regimens with current antiviral agents. Over the next 5 to 10 years, new agents will need to be proven active against a range of viral variants that are resistant to current PIs, less likely to cause the side effects associated with current PIs (eg. lipid abnormalities) and show a better bioavailability, such as in administration as prodrugs. If all, or a consistent part of, this is accomplished, a better care of HIV-infected individuals will be granted, thus resulting in a better quality of life and longer survival.
Bibliography

Papers of special note have been highlighted as of interest (*) or of considerable interest (**) to readers.


** Very interesting paper which demonstrated the efficacy of three-drug convergent combination therapy in inhibiting HIV-1 in vivo.


** Seminal paper which was the first to describe the emergence of drug resistance.


** First demonstration of a drug resistance pattern related to in situ mutagenesis procedures.


• Clearly describes the induction of nevirapine resistance following suboptimal therapy.


** Fundamental observation by a multicentric trial which demonstrated the superiority of highly active antiretroviral therapy versus two-drug regimens.


• The first demonstration of protease inhibitor (PI) cross-resistance.


• Seminal paper introducing the concept of the PI genetic barrier.

24. Winters MA, Chaparro JM, Lawrence J, Merigan TC. Human immunodeficiency virus type 1 protease genotypes and in vitro protease inhibitors susceptibilities of isolates from individuals who were switched to other protease inhibitors after long-term saquinavir treatment. J. Virol. 72, 5303–5306 (1998).


• Documents which points out the rationale of resistance testing in the clinical setting.
New HIV protease inhibitors for drug-resistant viruses – SPECIAL REPORT


Website


Affiliations

Stefano Rusconi
Cattedra di Malattie Infettive e Tropicali, Dipartimento di Scienze Cliniche “Luigi Sacco”, Università degli Studi, via G.B. Grassi 74, 20157 Milano, Italy
Tel: +39 023 904 3350
Fax: +39 025 031 9758
stefano.rusconi@unimi.it

Ottavia Viganò
Cattedra di Malattie Infettive e Tropicali, Dipartimento di Scienze Cliniche “Luigi Sacco”, Università degli Studi, via G.B. Grassi 74, 20157 Milano, Italy