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ANTIVIRAL DRUGS IN THE TREATMENT OF AIDS: WHAT IS IN THE PIPELINE ?

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Abstract
Drug development in the field of HIV treatment is rapid. New nucleoside analogues (NRTI), non-nucleoside analogue reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI) are currently being investigated in human trials. Furthermore, inhibitors of HIV attachment, fusion and integrase with novel modes of action are being developed, which offer new perspectives for the goal of a normalization of life-expectancy in HIV-infected individuals. The most advanced compounds likely to become licensed soon include the NNRTIs rilpivirine and etravirine, the integrase inhibitors raltegravir and elvitegravir, and maraviroc and vicriviroc, novel inhibitors of the CCR5 chemokine receptor, which functions as the major coreceptor for HIV-1.

INTRODUCTION

Highly active antiretroviral therapy (HAART) has markedly reduced the mortality of HIV-1 infected patients [1; 2]. Combinations of two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleosidic inhibitor of reverse transcriptase (NNRTI) have set the standard for HAART. The continuation of therapy for decades with the aim of normalizing life expectancy, however, is hampered by issues of toxicity, adherence, and the development and transmission of resistance. Despite the high number of licensed compounds, considerable cross-resistance within the drug classes and pharmacodynamic as well as pharmacokinetic interactions limit the number of combination options. HAART modifications in previously untreated subjects are primarily required due to toxicity and aherence [3], but virological failure remains an issue. Therefore, new drugs have to be developed for reduced toxicity, improved ease of administration, and a more robust antiviral effect.

NRTIs, NNRTIs, and PIs have the advantage of long-term clinical experience with the drugs and a proven prognostic benefit. Therefore, the development of novel compounds from within existing drug classes is promising. They should exhibit toxicity profiles different from the available drugs, be easy to administer and have activity against resistant variants. Furthermore, in order to improve virological response following resistance development, novel classes exploiting new targets in the viral replication cycle or even targeting immune responses have to be developed. Continued drug development serves the ultimate goal of normalization of life expectancy.

METHODS

Drug development in the field of HIV infection is highly competitive, and a company's decision to pursue or discontinue the development of a drug is driven by economic rather than scientific considerations. Of all candidate compounds, only a few reach the level of trials in humans, and some exhibit lack of efficacy or toxicity problems at this stage. Some compounds also have no obvious advantage over currently available ones, so that their development is discontinued.

Confidentiality of drug development within pharmaceutical companies and frequent renaming make it very difficult to trace the compounds and summarize the current state. Furthermore, the discontinuation of development is not always announced in the public.

Therefore, for the purpose of this review the compounds were categorized as

Category 1: Compounds that are in phase II or have passed phase II successfully
Category 2: Compounds that are either in or have passed phase I
Category 3: Drugs that have not yet been investigated in human trials ("preclinical"), but for which published manuscripts, conference abstracts, or internet or press reports after January 2005 indicate the continuation of drug development. Only publicly accessible information was evaluated. In the list of Category 3 compounds, no drug classes but only individual lead compounds were included.

Drugs like amdoxovir and brecanavir are listed separately, because their development was discontinued during studies in humans.

The data was acquired by searching scientific databases (EntrezPubMed http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed, conference abstracts, company homepages, and public patent registries.

Category 1 and 2 compounds are regarded as candidates for further development, category 3 drugs are not discussed below.

This review summarizes the status in the field as of August 2007.

The Most Promising New Antivirals

1. Nucleoside Reverse Transcriptase Inhibitors and Related Compounds

A hallmark feature for new NRTIs should be high activity against NRTI-resistant variants, especially those carrying the M184V mutation. Apricitabine and elvucitabine have demonstrated antiviral activity in clinical trials [4-6]. For apricitabine, activity against NRTI-resistant strains was already confirmed in a pilot trial [5]. That remains to be shown for elvucitabine. Both are the most promising compounds within this class. The antiviral activity of racivir in a pilot trial in subjects with lamivudine-resistant virus was limited but significant [7]. Its similarity to emtricitabine, however, could jeopardize its further development.

Unlike other NRTI, KP-1461 utilizes error induction in the reverse transcriptase as a mechanism of action. A phase IIa study has just begun and will soon reveal the potential of this approach.

Since zidovudine is licensed and problematic due to its side effect of lipodystrophy, fozivudine-tidoxil as its prodrug has little chance for further development. Similarly, since the parent compound of fosalvudine, alovudine (MIV-310) was discontinued due to the limited effect on multi-drug resistant virus, fosalvudine is unlikely to succeed. However, in December 2006, Medivir outlicensed alovudine to Presidio Pharmaceuticals, so that the fate of the compound remains unclear.

2. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTI)

Tibotec has developed rilpivirine as a first-line NNRTI with similar activity to efavirenz, probably less neuropsychiatric toxicity and less blood lipid elevation [8-10]. The drug is active *in vitro* against variants carrying key NNRTI resistance mutations and requires more mutational steps for a marked reduction of sensitivity than efavirenz or nevirapine. According to current trial results, the compound has a high potential for first-line therapy. It might be very helpful in the setting of increasing rates of transmitted NNRTI resistance mutations.

Another Tibotec drug, etravirine, is also active against NNRTI-resistant strains and has the potential to add significant activity to salvage regimens, as demonstrated by the DUET-1 and -2 trial results in subjects with treatment failure and resistance [11; 12]. Unless unexpected toxicity issues appear in the trials, both drugs are currently the most promising candidates for licensure. UK-453,061 by Pfizer continues to be investigated, whereas the fate of GW695634 by GSK is less clear. BILR 355 BS requires ritonavir boosting, which would probably restrict it to a small segment of the market.

3. Protease Inhibitors

Several protease inhibitors are not being developed any longer (see Table 5). PPL-100 as a pro-drug of PL-100 is currently investigated in humans (in a cooperation of Merck and Ambrilia Biopharma) [13; 14]. A unique feature of this compound is its potential to boost the levels of other drugs similar to ritonavir, which could make it attractive, provided it is not more toxic than ritonavir.

4. Integrase Inhibitors

After investigation into the details of the different steps of viral integration over several years, the principle of strand transfer inhibition has now led to the development of highly active antivirals. The Merck compound raltegravir has exhibited excellent antiviral activity in both salvage therapy and treatment-naïve subjects [15-17]. Its independence from ritonavir boosting makes it attractive for all lines of therapy, although it has to be administered twice daily. In contrast, elvitegravir by Gilead requires ritonavir boosting but in turn can be dosed once daily. It is active in treatment-experienced patients [18] and appears very promising, too. Raltegravir is somewhat ahead in terms of clinical trial results and will most likely be licensed earlier than elvitegravir. Unfortunately, cross-resistance between these two compounds is likely.

5. Chemokine receptor Blockers

Drugs that block the binding of HIV-1 to either the CCR5 or the CXCR4 receptor have theoretical advantages over those mentioned above: 1. they aim at a cellular target that does not underly mutational changes in the individual host and 2. they act extracellularly, making them independent from cellular uptake, activation and efflux mechanisms. CCR5 receptor blockers are focussed on in other reviews in this issue of the journal. In contrast to CCR5, however, there is no biological analogy to CXCR4 blockade. This raises concerns regarding side effects. The development of CXCR4 blockers has indeed been hampered by unexpected toxicities such as the dose-dependent leukocytosis induced by AMD070. This compound is now also being investigated as a haematological agent. It therefore appears questionable if CXCR4 blockers will be developed until licensure.

6. Attachment and Fusion Inhibitors

The humanized monoclonal antibody TNX-355 directed against the CD4 molecule developed by Tanox is the most advanced attachment inhibitor. It has shown a clear antiviral effect [19; 20]. Due to its parenteral mode of application, however, it is unlikely to become attractive for any line of therapy before salvage. The availability of other novel compounds for salvage therapy further reduces the likelihood that any infused antibody would be used to a relevant extent. Sifuvirtide by FusoGen, a Chinese company, is being developed within China. It appears similar to enfuvirtide in its pharmacologic properties and might become a locally propagated drug such as phosphazid in Russia.

An interesting compound is being developed by Samaritan Pharmaceuticals, recently in cooperation with Pharmaplaz: SP-01A inhibits host cell membrane events that are required for fusion. It is active against

Table 1. Reverse Transcriptase Inhibitors and Protease Inhibitors in Development.

Class	Compound	Company	Potential/drawbacks	Development status	Cate-irgory	Recent references
NRTI	Racivir	Pharmasset	Racemic mixture of +- and --emtricitabine, active against M184V mutants and HBV	phase II	1	Cahn 2007(7)
	Apricitabine (AVX 754, BCH10618, (-)dOTC, SPD754)	Avexa Pharmaceuticals	Active against M184V strains, PK interaction with 3TC	phase II	1	Cahn 2006(4) Cahn 2007(5)
	Elvucitabine (ACH-126,443)	Achillion Pharmaceuticals	Active against NRTI-resistant strains and HBV	phase II	1	Dutschman 2004(26) Colucci 2006(6)
	MIV-210 (FLG)	Medivir, GSK	active against HIV and HBV	phase II	1	internet report 2005(27)
	Fozivudine tidoxil	Heidelberg Pharma/ GlaxoSmith Kline	zidovudine prodrug	phase II	1	Bogner Girard 1997(28;29), 2000(30)
	Fosalvudine	Heidelberg Pharma	alovudine prodrug (see table 4)	phase II	1	internet report 2007(31)
	KP-1461 (SN1461)	Koronis Pharmaceuticals	error induction in viral RT, "lethal mutagenesis", prodrug of SN1212	phase II	1	Harris 2005(32)
	Stampidine	Parker Hughes Institute	primarily investigated as microbicide, systemic activity in animal models (FIV)	preclinical	3	Uckun 2005-2007(33-36)
	Dioxolanthymidin (DOT)	Emory University	Activity against NRTI-resistant strains	preclinical	3	Lennerstrand 2006(37)
	D-FDOC	Emory University	Activity against HIV and HBV	preclinical	3	Hernandez-Santiago 2005(38)
	4'-Ed4T	Kagoshima University	Activity against resistant variants	preclinical	3	Tanaka 2005, Nitanda 2005, Yang 2007(39-41)
	E2FdA	Kumamoto University	Activity against resistant variants	preclinical	3	Nakata 2006(42)
	Thiovir	Adventrx Pharmaceuticals	oral broad antiviral agent, comparable to foscarnet	preclinical	3	Waninger 2005(43)
NtRTI	GS9148	Gilead	Active against TAM strains	Preclinical	3	Cihlar 2006(44)
NNRTI	Rilpivirine (TMC-278)	Tibotec / Janssen & Janssen	high antiviral activity in 1st line ART, less neuro-psychiatric toxicity than efavirenz	Phase III	1	Ruxrungtham 2007(10), Pozniak 2007(8;9)
	Etravirine (TMC-125)	Tibotec / Janssen & Janssen	active against NNRTI-resistant variants	Phase III	1	Lazzarin 2007 and Madruga 2007; (11;12) Mills 2007, Katlama 2007 (45;46)

Table 1 continued

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Class	Compound	Company	Potential/drawbacks	Development status	Cate-irgory	Recent references
	UK-453,061	Pfizer	Active against NNRTI-resistant virus	Phase Ib/II	1	Fätkenheuer 2007(47)
	GW695634	GlaxoSmithKline		Phase II	1	Becker 2005(48)
	Calanolide A	Sarawak MediChem Pharmaceuticals	made from rainforest plant, company announced phase II studies announced for 2005	Phase Ib, continuation unclear	2	Eiznhamer 2002, Creagh 2001 (49;50)
	BILR 355 BS	Boehringer Ingelheim	RTV-boosted	phase I	2	Coulombe 2005(51)
	MIV 170	Medivir	development cooperation with BMS terminated in 2007	preclinical	3	Review(52)
	RD4-2217	Tosoh / Yamanouchi Pharma	more active against resistant strains	preclinical	3	Kodama 2005(53)
	IQP-410 (54)	ImQuest Pharmaceuticals / Samjin	also interferes with HIV entry	preclinical	3	Buckheit 2001(55), Internet communication(56)
	R1206	Roche	active against NNRTI-resistant variants, prodrug of R0355	preclinical	3	Klumpp 2007(57)
	Triol	Oswaldo Cruz Foundation	naturally occurring diterpene	preclinical	3	Cirne-Santos 2005(58)
	IDX12899	Idenix Pharmaceuticals	resistance selection profile different from efavirenz	preclinical	3	Jakubik 2007(59)
Protease inhibitors	PPL-100 (prodrug of PL-100)	Merck / Ambrilia Biopharma	Long half-life, could boost levels of other PIs.	phase I	2	Wu 2006(13;14)
	P-1946	Pharmacor	Active against PI-resistant variants	preclinical	3	Sévigny 2005(60)
	SPI-256	Sequoia	Active against PI-resistant variants	preclinical	3	Gulnik 2006(61)
	SPI-390	Sequoia	Active against PI-resistant variants	preclinical	3	Afonina 2007(62)
	SPI-457	Sequoia	Active against PI-resistant variants	preclinical	3	Afonina 2007(62)
	GRL-02031	Kumamoto University	high activity against resistant variants	preclinical	3	Koh 2006(63)
	UIC-02031	Kumamoto University	active against resistant variants	preclinical	3	Koh 2005(64)

resistant strains and is currently in a phase II trial. The development of this agent deserves special attention.

7. Immune Therapy and Other Cellular Targets

The broadly neutralising monoclonal antibodies 2F5, 3A4, and 2G10 developed by Katinger and colleagues in Vienna have demonstrated antiviral activity in clinical trials [21; 22], especially when applied together. As with other antibody preparations, however, their mode of application makes continued development and clinical use as an antiviral therapy unlikely. HRG, a polyclonal anti-HIV serum from New Zealand, has the additional problem of being

Table 2. Inhibitors of HIV integrase and maturation, zinc finger and DNA polymerase inhibitors.

Class	Compound	Company	Potential/drawbacks	Development status	Category	Recent references
integrase inhibitors	raltegravir (Isentress, MK-0518)	MSD	no RTV boosting required, bid dosing	phase III	1	Markowitz 2007(15); Cooper 2007, Steigbigel 2007 (16;17)
	elvitegravir (GS-9137, JTK-303)	Gilead Sciences / Japan Tobacco	optimal PK profile requires RTV boosting	phase II/III	1	Zolopa 2007(18)
	BMS 707035	Bristol Myers Squibb		phase Ib, phase II trial terminated	2	Internet report(65)
	GSK 364735	GSK / Shionogi		phase I	2	Reddy 2007(66)
	Dicaffeoylquinic acid	Academy of Military Medical Sciences, China	drug extract from chinese herbs, active against HIV and HBV	phase I/II	2	Internet report(67)
maturation inhibitors	Bevirimat (PA-457)	Panacos	blocks last step in Gag processing; problems with galenic preparation	phase II	1	Li 2003(68), Mc Beatty 2005(23), Smith 2006(25), Callister 2007(69)
	PA1050040	Panacos	not crossresistant with PA-457	phase I	2	Kilgore 2007(70)
	UK-201844	Pfizer		preclinical	3	Blair 2006(71)
zinc finger inhibitors	HPH116 (micronized Azodicarbon-amide, ADA)	H-Pharmaceuticals, Rega Institute Leuven	glucose elevations reported with old galena form	phase I/II	2	Rice 1997(72),) Goebel 2000(73), internet report(74
polymerase inhibitors	MIV-410	Medivir		preclinical	3	press release (75)
	NcRTI-1	Gilead	blocks DNA polymerase activity of HIV RT	preclinical	3	Ehtesvami 2006(76)

generated by immunization of goats with HIV proteins.

The application of MDX-10, a human anti-CTLA4 antibody, is a fascinating new approach to improve the cytotoxic T lymphocyte response to HIV-1 *in vivo*. This concept is also being investigated in tumour research. HIV studies have just begun, and no results are available as yet.

Bevirimat and PA1050040 by Panacos represent the promising new class of maturation inhibitors. Bevirimat has an *in vivo* antiviral effect [23-25], the magnitude of which remains to be assessed in current phase II studies.

The potential of HPH116, the new galenic formulation of the zinc finger inhibitor azodicarbamide, remains to be assessed.

Summary and Perspectives

New drugs for HIV treatment are being developed within big pharmaceutical companies as well as within smaller biotech companies that subsequently outlicense them. This process allows for a rapid development of novel compounds and an efficient selection of those that really meet therapeutic needs and are likely to be successful. The long list of compounds in preclinical development (category 3) illustrates the continuously high research activity in the field that is stimulated by the successes of HAART, the requirement for life-long therapy, and the global scale of the HIV problem.

New developments within existing drug classes (e.g. rilpivirine and etravirine) have the advantage of proven beneficial effects of established compounds in the class. Finally, strand inhibition in the process of viral integration has offered a target for the new class of integrase inhibitors, which have been very successful to date. The potential of other approaches such as zinc finger inhibition (azodicarbonamide) or maturation inhibition is less clear.

Since the development of the fusion inhibitor enfuvirtide, approaches aiming at early steps in the viral lifecycle, have led to new developments. Among those, the

Table 3. Inhibitors of HIV Attachment, Entry and Fusion.

Class	Compound	Company	Properties/potential/ drawbacks	Development status	Category	Recent references
Attachment inhibitors	TNX-355 (mAb 5A8)	Tanox	Humanized murine α-CD4 mAb, Intravenous application	phase II	1	Kuritzkes 2004, Zhang 2006, Norris 2006 (19;20;77)
	KRH-3955	Kureha Inc.		preclinical	3	Tanaka 2006(78)
	KRH-3140	Kureha Inc.		preclinical	3	Tanaka 2006(78)
CCR5 blockers	Vicriviroc (SCH-D, 417690)	Schering-Plough	antiviral effect in ART-naïve subjects inferior to efavirenz if unboosted, requires RTV boosting for optimal effect	Phase III	1	Schürmann 2007(79), Gulick 2007(80)
	INCB009471	Incyte	high antiviral activity in vivo	Phase II	1	Cohen 2007(81)
	Pro 140	Progenics Pharmaceuticals	Monoclonal antibody, intravenous administration	Phase II	1	Saag 2007(82)
	CCR5mAb004	Human Genome Sciences	Monoclonal antibody, intravenous administration	Phase I	2	Giguel 2006(83)
	Ro1752	Roche	active against maraviroc-resistant strains	preclinical	3	Jekle 2007(84)
	AMD-887	Genzyme (Anormed)		preclinical	3	Schols 2005(85)
	TAK 652	Takeda / Tobira		preclinical	3	Baba 2005(86)
CXCR4 blockers	AMD070 (AMD11070)	Genzyme (Anormed)	dose-dependent leukocytosis	phase I, on hold	2	Moyle 2007(87), Saag 2007(88)
	KRH-2731-5HCI	Kureha Corp.		preclinical	3	Murakami 2004 (89), Castagna 2005(90)
	KRH-3140	Kureha Corp.		preclinical	3	Tanaka 2006(78)
	KRH-3955	Kureha Corp.		preclinical	3	Tanaka 2006(78)
Fusion Inhibitors	FP-21399	Lexigen (Fuji Immuno Pharmaceuticals)	skin discolorations, development probably discontinued	phase II	1	Zhang 1997(91), Dezube 2000, Poli 2001(92;93)
	Sifurvitide	FusoGen Pharmaceuticals	chinese development, similar to enfuvirtide, parenteral administration	phase II	1	Dai 2005(94,) Internet communication 2007(95
	TRI-291144	Trimeris / Roche	more convenient than enfuvirtide and not cross-resistant	preclinical	3	Internet communication(96)
	SPC3	Ambrilia	Synthetic peptide, intravenous administration, failed as microbicide	phase I	2	Internet communication(97)
cell membrane stabilizator	SP-01A	Samaritan Pharmaceuticals / Pharmaplaz	Inhibits host cell membrane events required for entry, active against resistant strains	phase II	1	Internet communication(98)
CCR5 down-regulator	Aprepitant (EmendR)	MSD	licensed as antiemetic, downregulates CCR5 expression	phase I	2	Wang 2007(99)
gp41 inhibitors	Virip	IPF Pharma Ceuticals	inhibitory peptide from human plasma	preclinical	3	Munch 2007(100)

Table 4. Drugs with other modes of action

Class	Compound	Company	Properties / potential / drawbacks	Development status	Category	Recent references
CTLA4 inhibitor	MDX-010	Medarex	human anti-CTLA4 antibody, improvement of HIV-specific T-cell responses	phase I	2	Langer 2007(101), press release(102)
DHS inhibitor	Semapimod (CNI-1493)	Cytokine PharmaSciences	targets Rev indirectly via inhibition of deoxyhypusine synthase	preclinical	3	Hauber 2005(103)
Nuclear import inhibitor	ITI-367	International Therapeutics	prevents nuclear trans-loaction of the HIV-1 pre-integration complex	preclinical	3	Haffar 2005(104)
neutrali-zing antibody	HRG	Virionyx, Auckland	goat anti-HIV serum	phase I	2	Dezube 2003 (105), Sanford 2005(106)
	2F5, 3A4, 2G10	Universität für Bodenkultur Wien	broad neutralization capacitiy, antiviral effect in	phase II	1	Trkola 2005(22), Manrique 2007(21)
	KD-247	Kumamoto University	broad neutralization capacity	preclinical	3	Yoshimura 2005(107)

Table 5. Drugs that were discontinued during/after human studies.

Class	Compound	Company	Reason for discontinuation	status at discontinuation
NRTI	Zalcitabine (ddC)	Roche	Neuropathy, insufficient efficacy, withdrawn from market	licensed
	Reverset (dd4FC, DPC-817, DFV, dexelvucitabine)	Incyte/Dupont / Bristol Myers Squibb / Pharmasset	pancreatic toxicity, 3TC antagonism	phase II
	Amdoxovir (DAPD)	RFS Pharm/Gilead	Ocular toxicity	phase II
	Alovudine (FLT, MIV-310)	Medivir / Presidio Pharmaceuticals / (Boehringer Ingelheim)	lack of efficacy	phase II
	Lodenosine (F-ddA)	US Bioscience	toxicity	phase II
	Lobucavir	Bristol Myers Squibb	cancerogenicity	phase II
	AVX-756 (SPD-756/ BCH-13520)	Avexa Pharmaceuticals/ Shire Biochemicals		phase I
NtRTI	Adefovir	Gilead	renal toxicity, little efficacy	phase II
	GS7340	Gilead	little efficacy	phase I
NNRTI	Capravirine	Pfizer	little efficacy	Phase II
	DPC-083 (BMS-561390)	Bristol Myers Squibb/Dupont	Too similar to efavirenz	Phase II
	Emivirine (coactinon)	Triangle	little efficacy	Phase II
	GW420867X	GSK	Unfavourable PK interactions	Phase II

Table 5 continued.

Class	Compound	Company	Reason for discontinuation	status at discontinuation
NNRTI	GW695634	GSK	Antiviral efficacy inferior to other NNRTI	Phase II
	TMC-120	Tibotec Virco/ Janssen & Janssen	Inferior to TMC-125	Phase II
Protease Inhibitors	Amprenavir	GSK	Withdrawn from market due to better bioavailability of successor compound fosamprenavir, pediatric formulation still available	Licensed
	Fortovase (saquinavir soft gelatine capsules)	Roche	development of saquinavir 500 mg capsules	Licensed
	brecanavir	Bristol Myers Squibb	Low bioavailability	Phase II/III
	Mozenavir (DMP 450)	Triangle	Drug profile too similar to licensed compounds	Phase II
CXCR4 blockers	AMD-3100	Anormed (Genzyme)	Lack of efficacy	Phase II
CCR5 blockers	aplaviroc (GSK 873,140)	GSK / Shionogi	Hepatotoxicity	Phase II
	Ancriviroc (SCH C)	Schering Plough	Insufficient antiviral efficacy	Phase II
Entry inhibitors	PRO 542	Progenics	unknown	Phase II
	T-1249	Trimeris / Roche	Manufacturing problems	Phase II
Integrase inhibitors	L870,810	MSD	Hepatic and renal toxicity in dogs	Phase II

CCR5 inhibitor maraviroc has recently been licensed. The long list of compounds under investigation demonstrates the opportunities in this field.

With more compounds being available, the strategic position of these drugs in the therapeutic sequence becomes more and more important. For a novel compound, antiviral activity can be demonstrated most easily in the setting of resistant virus during salvage therapy or as monotherapy, the latter being problematic if there is a potential for cross-resistance to licensed drugs. Therefore, most compounds have to be tested in salvage therapy first in order to assess their potential, with the associated problems of pharmacokinetic interactions with other drugs.

In earlier lines of therapy they compete with well tolerated licensed drugs with high activity and a track record of clinical experience over many years. Therefore, it is going to be more and more difficult for novel compounds to prove non-inferiority and advantages over licensed drugs in terms of toxicity and ease of administration over a sufficiently long period of time, generally a minimum of 48 weeks. Probably several of the drugs listed in this review will fail these criteria.

For patients with HIV-2 infection, only a fraction of these therapeutic approaches is promising. Many currently licensed compounds are inactive against HIV-2. More so, none of these novel approaches is being developed specifically for HIV-2. Even though they represent a small minority in developed countries, the higher numbers of HIV-2 infected subjects in less developed countries require an extension of drug development to HIV-2.

Despite considerable successes in HIV-1 therapy, some therapeutic needs remain unmet. Continued therapeutic progress is needed and depends on drug development by the pharmaceutical and biotechnological industry. However, as may be learned from past mistakes and failures, clinicians have to optimize the strategic use of current and new drugs in order to exploit their potential for the benefit of the patients.

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