The Rationale and Development of New Drugs to Treat HIV Infection

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Abstract: Fewer than one million HIV infected individuals are currently receiving antiretroviral therapy. Present antiretroviral therapy costs between $10,000 and $20,000 per year, which provides excellent value for money in developed countries with a cost of about $10,000 per life year saved; this compares very favourably with other therapies in chronic use. Recent studies have demonstrated a dramatic decline in HIV and AIDS related morbidity and mortality across developed countries and these reductions have been sustained since the introduction of highly active antiretroviral therapy (HAART) since 1996. The use of HAART has been associated with specific toxicities related to the drug class, problems with adherence with the subsequent emergence of viral isolates and resistance associated mutations. The replacement of older therapies with newer drugs that avoid cross resistance even within the same class of antiretroviral, represents a new hope in retroviral targeting.

INTRODUCTION

Old Drugs and Resistance

The principles of the treatment of HIV infection were developed concomitantly as a result of large randomised clinical controlled trials and because of the increasing understanding of the dynamics of HIV replication [1-6]. Like many other RNA viruses, HIV replicates at a staggering rate and is capable of producing 10 [9] particles of virus per day [7], resulting in the potential production of viral progeny with every potential single and double mutation within the viral genome being produced each day [8]. Some of these mutations have reduced sensitivity to individual drugs or drug classes used to treat HIV infection and suppress viraemia; thus resistant mutations may be selected very rapidly to monotherapy [9].

Randomised clinical controlled trials have shown that combinations of antiretroviral drugs prolong life and delay the development of viruses with reduced sensitivities to drugs [10-14]. The advent of potent therapy, which allowed complete viral suppression, resulted in resistance not being selected during the initial phases of introduction of treatment and lack of emergence of resistance at a significant rate while that drug therapy is successfully continued. Thus, the established dogma is that antiretrovirals should be used in combination and should be sufficiently potent to suppress viral replication completely [15]. In the future, this dogma may be challenged as some drugs are being developed where single agents are so potent and have such complicated genetic patterns associated with their resistance that it may be possible that a single agent would prove effective.

The concept of antimicrobial resistance is not new and was first described with the use of antibiotics [16]. More recently, this problem is becoming apparent with the use of antiviral agents and has been described with the use of both anti-hepatitis-B virus and anti-herpes virus agents [17-20]. However, it is most commonly observed with the treatment of HIV-1 infected patients receiving HAART.

Resistance to antiretroviral therapy has been documented for each of the three main classes of drugs currently available, the nucleoside-reverse-transcriptase-inhibitors (NRTIs), non-nucleoside-reverse-transcriptase-inhibitors (NNRTIs) and protease-inhibitors (PIs) [21]. Resistance associated mutations in the reverse-transcriptase (RT) and protease (Pr) genes are associated with reduced virological response. Once these strains have appeared in the host population, there exists the possibility of transmission of such viruses to new hosts, previously naïve to antiretroviral therapy [22]. In such individuals, response to antiretroviral therapy may be suboptimal [23].

Resistance associated mutations are classified as primary if their presence alone confers resistance to a particular drug. Mutations which compensate for the fitness of the virus in the presence of these mutations are classified as secondary. Reports of the estimated prevalence of antiretroviral drug associated HIV resistant strains in treatment-naïve individuals vary from rates of 0.8% for NNRTI resistance mutations to over 25% [24].

Drug development continues apace, both to improve upon existing molecules and the drug discovery for agents active against new sites in the HIV replication cycle. Particularly advanced are those drugs which act against the process of viral attachment to the cells and subsequent fusion and release of the contents of the virus into the cell. One reason to develop new drugs is to improve on potency of the present compounds, although there are few data to suggest this is really necessary. One of the early hopes of antiretroviral therapy was that treatment sustained for several years might eradicate all evidence of the virus and allow therapy to be discontinued. This hope has not been realised because latent virus also exists in sanctuary sites and can re-emerge when drug cessation has stopped [25-30]. Such sanctuary sites may be anatomical such as the brain, testis,

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kidney or the virus may exist in a truly latent state in resting cells; in addition, the virus may be replicating slowly in a group of cells which are largely inaccessible to present pharmaceutical agent [31].

The two most practical reasons for new drug development are improving adherence and reducing the toxicity of present regimes [32-37]. The politically correct term for what used to be known as compliance, that is to say the ability of the patient to continue therapy despite side effects long term, has changed recently to either adherence or concordance in recognition of the fact that patient and clinician require a consensus view regarding the importance of drug therapy and that there is an obligation on the doctor and those developing drugs to make them easy to adhere to. Adherence is however, relatively poor in all therapeutic areas where long term drug therapy is required. The reasons for this are complex and include personal beliefs about the dangers of chemicals entering the body which are difficult to alter. However, there are a number of practical issues which can make drug adherence easier. There are clear data that three times a day treatments are difficult to adhere to in the long term and that exacting food requirements (some drugs need to be taken with food and some on an empty stomach) make this even more difficult. Thus, the Holy Grail of drug research at the moment is to try and produce agents which can be taken once a day with the presence of food having little or no effect on absorption. Although it is unkown that such regimes are better adhered to than those taken twice a day, reversible momentum has been created that this is the best way forward [38-45].

Most of the toxicities of antiretroviral therapy which cause concern, were not appreciated at the time that such drugs were licensed on the basis of large 48 week studies [46]. It is now widely appreciated that nucleoside analogues, the back-bone of HAART also have effects on mitochondrial DNA. In human cells, mitochondrial DNA appears to be depleted as a result of HIV infection *per se* and some nucleosides, particularly the dideoxynucleosides, exacerbate this process [47]. This results in a number of side effects which can be life threatening or disabling with a propensity to affect those tissues containing slowly dividing cells (eg brain, muscle as opposed to the gut).

Perhaps, most common is a peripheral neuropathy followed by pancreatitis, but an occasional lethal side effect (much reduced in incidence with the dideoxynucleosides, particularly when used in combination, eg d4T and ddI) is lactic acidosis [35, 48-51]. Here, the liver becomes incapable of clearing lactic acid produced as a result of exercise and is associated with marked disturbance of acid based balance. For patients, the most stigmatizing effect of many antiretrovirals currently in use is the loss of subcutaneous fat particularly around the face which produces a 'haggard' appearance. How close this is related to a generalised disorder of lipid metabolism with increasing visceral fat and an abnormal lipid profile is controversial as the drugs are most intimately involved in this process [35, 52]. Unlike lactic acidosis, it does appear that the process is accelerated using the dideoxynucleoside analogues particularly d4T, in comparison with other nucleosides. Abnormalities of drug lipids appear to be associated with the present generation of proteinase inhibitors (PIs), which are probably the most single potent agents available to treat HIV infection at present. Loss of subcutaneous fat, accumulation of visceral fat and lipid abnormalities, often associated with increased insulin resistance, have been grouped together and called the fat redistribution syndrome [52-56]. This appears to be commoner with PI therapy and it may well be that nucleoside analogues have a synergistic effect with PIs to produce this syndrome.

Currently, there are 18 drugs licensed for the treatment of HIV infection (Table **1**). Despite this, there is a need for new antiretroviral agents active against HIV-1 strains harbouring resistance associated mutations. The selective targeting of different sites in HIV-1 viral replication from the main three classes of currently available therapy may provide agents active against viral stains resistant to current therapy. The first fusion inhibitor enfuvirtide, has recently been licensed in the US and Europe. Both integrase-inhibitors and CCR5-receptor inhibitors are currently undergoing phase II/III clinical trials.

Table 1. Currently Approved Antiretroviral Drugs

HIV reverse transcriptase inhibitors
Nucleoside analogues
zidovudine (ZDV, AZT)
didanosine (ddI)
zalcitabine (ddC)
stavudine (d4T)
lamivudine (3TC)
abacavir (ABC)
emtricitabine (FTC)
Nucleotide analogues
tenofovir (TDF)
Non-nucleoside reverse transcriptase inhibitors (NNRTI)
nevirapine (NVP)
efavirenz (EFV)
HIV protease inhibitors
saquinavir (SQV)
ritonavir (RTV)
indinavir (IDV)
nelfinavir (NFV)
amprenavir (APV)
lopinavir/ritonavir (LPV/r)
atazanavir (ATV)
Fusion inhibitors
enfuvirtide (T-20)

Also in development are novel NRTIs, NNRTIs and PIs active against viral strains resistant to the currently available agents in these classes Table **2**). This remainder of this review article will focus on new agents in these three classes currently in phase II/III development.

NEW DRUGS

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Reverse transcriptase inhibitors are of two sorts. Firstly, there are those which act as analogues of naturally occurring

Table 2. Important Investigational Antiretroviral Drugs in Phase II/III Development

HIV reverse transcriptase inhibitors
Nucleoside analogues
amdoxovir (DAPD)
elvucitabine (ACH-126)
Non-nucleoside reverse transcriptase inhibitors
capravirine (Ag 1549)
TMC 125
HIV protease inhibitors
tipranavir (TPV, PNU-140690)
TMC 114

nucleosides and these in turn act as chain terminators. Secondly, there are a diverse array of chemicals known as non nucleoside reverse transcriptase inhibitors, which act in a pocket of the reverse transcriptase close to the catalytic site [57-59]. The Achilles heel of these latter compounds is that only one mutation is required in this pocket to produce virus with markedly reduced sensitivity to these drugs. NRTIs are an integral component of nearly all antiretroviral treatment regimens. These agents cannot support continued synthesis of a newly made DNA strand and thereby act as chain terminators of the polymerisation process catalysed by the HIV reverse transcriptase. The biggest challenge for new agents is cross-resistance with pre-existing drugs. The development of novel NRTIs with limited or no cross-resistance is the goal for new agents.

Tenofovir DF disoproxil fumarate (*R*-9-(2-phosphonyl-methoxypropyl)adenine; tenofovir DF) was the first nucleotide analogue reverse transcriptase inhibitor to be approved for the treatment of HIV infection. It has been well tolerated in clinical trials to date, without evidence in cohort studies of long-term toxicity, including the mitochondrial toxicity that has been associated with some nucleoside analogue reverse transcriptase inhibitors. Following its approval in October 2001, tenofovir DF has quickly become a widely used component of antiretroviral regimens for both treatment naïve and experienced patients. Recent data also indicates that it is able to overcome lamivudine resistance in the treatment of hepatitis B [20, 60, 61].

Agents in development are discussed as follows:

Elvucitabine (ACH-126)

Elvucitabine (ACH-126 443, L-d4FC) is a L-cytidine analogue with activity against HIV resistant strains resistant to several other NRTIs including zidovudine and lamivudine and is also active against hepatitis B virus. The L-nucleoside configuration of the compound may provide protection against mitochondrial toxicity; a serious side effect often seen with D-nucleosides.

In healthy volunteers, dose-proportional pharmacokinetics following a single oral dose in the 5 to 100 mg range were observed with a half-life of four hours [62]. In a study in treatment-experienced HIV infected individuals with known viral strains harbouring the M184V mutation in RT, elvucitabine was dosed at 50 or 100 mg/day for up to 28 days [63]. A mean drop in plasma HIV RNA of 0.67 and 0.78 log copies/mL was observed for the 50 and 100 mg dose, respectively. However, further dosing was stopped due to bone marrow toxicity in several patients and a decline in CD4+ lymphocyte count. Further studies to assess lower dosed of elvucitabine are planned.

Amdoxovir (DAPD)

Amdoxovir (diaminopurine dioxolane, DAPD) is a guanosine analogue which has also shown *in vitro* activity against HIV-1 and hepatitis B virus. The active form of the drug, dioxolane guanine (DXG) has a greater activity than amdoxovir and is formed after intracellular deamination. Amdoxovir shows some level of *in vitro* activity against viruses harbouring mutations associated with zidovudine and lamivudine, as well as strains harbouring the multi-NRTI resistant insertion mutation at codon 69 [64, 65]. However, viral strains with the K65R mutation in RT associated with tenofovir, abacavir and didanosine use and strains with the L74V mutation associated with didanosine and abacavir use have been shown *in vitro* to have reduced susceptibility to amdoxovir [66].

Toxicological studies have revealed obstructive nephropathy secondary to crystallisation of this agent in the renal tubules in animals and lens opacities in both animals and humans. In a randomised study of 18 HIV-infected heavily treatment experienced individuals with a median of five NRTI-associated mutations, a new antiretroviral regimen was chosen based on the results of an HIV resistance test and amdoxovir added to this regimen at either 300 mg or 500 mg twice daily. After 12 weeks on this therapy, plasma HIV RNA decreased by a mean on 1.5 and 0.75 log copies/mL in the 500 and 300 mg groups, respectively [67]. In five subjects, lens opacities were demonstrated during the study, however, baseline evaluations were not performed. Currently, clinical studies are on hold awaiting further safety data.

Alovudine (MIV-310)

Alovudine (3'-deoxy-3'-flourothymidine, MIV-310, FLT) is a pyrimidine nucleoside analogue, with some similarities to zidovudine and lamivudine. Alovudine was initially tested in the early 1990s. However, development was halted because of haematological safety concerns in doses above 10 mg/day and no obvious advantage over zidovudine [68]. More recently, alovudine was tested against a large panel of multi-resistant HIV variants and found to have a potent and unique profile *in vitro* [69].

In a recent study, alovudine at 7.5 mg once daily was added to a failing antiretroviral regimen in 15 HIV-infected individuals with at least two thymidine-associated mutations (TAM) [70]. After four weeks of therapy, median decrease in viral load was -1.13 log copies/mL. Of interest, the median reduction was only -0.57 versus -1.88 log copies/mL in patients also receiving stavudine versus those not on stavudine. A viral load drop of -1.6 and -1.88 log copies/mL was observed in individuals with two or three TAM and four or five TAM respectively. No serious adverse events were observed using this lower dose from previous studies.

Further studies with different dosages and longer administration times are planned.

Racivir

Racivir ((±)-β-2',3'-dideoxy-3'-thia-5-fluorocytosine, (±)-FTC or RCV) is a 50:50 mixture of the two β-enantiomers of FTC being developed by Pharmasset. This compound is a racemic FTC (qv) mixture (Fig. **3**). In 2001, preclinical data were published showing that racivir was at least as potent in its antiviral activity as emtricitabine in the HuPBMC-SCID mouse model of HIV infection. Further data reported also showed that racivir and emtricitabine had dose-dependant antiviral activity in the HuPBMC-SCID mouse model of HIV-1 infection. The pharmacodynamic modelling of the viral load data indicated a marked advantage for racivir over emticitabine [71]. In a phase 1 study, the mean peak plasma concentration was >100 times the EC90 (concentration required to reduce virus replication by 90%) for wild type HIV at the doses of 400 and 600 mg. The concentration of racivir at 24 hours was equal to 10 times the *in vitro* EC_{90} for wild type HIV-1. In this single dose study, all adverse events (AEs) were mild and occurred no more frequently than with placebo.

In a phase I/ II study in HIV-infected patients who were antiretrovirus-treatment-naive, racivir showed potent anti-HIV activity when given once a day in combination with stavudine and efavirenz [72]. The antiviral effect lasted more than two weeks after the drugs were stopped. It is currently in phase II clinical trials designed to measure its efficacy in patients harbouring lamivudine-resistant virus.

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Although currently marketed NNRTIs are highly selective and extremely potent, they rapidly select for resistant virus. Moreover, single mutations can lead to dramatic reductions in susceptibility, often to all available inhibitors within the class [73]. This broad cross-resistance prevents the consecutive use of current NNRTIs in treatment regimens. Next-generation agents with activity against NNRTI-resistant isolates would therefore offer new treatment options.

Capravirine

Capravirine (formerly known as "S-1153" and "AG-1549") is an imidazole NNRTI and may be an attractive alternative to currently available NNRTIs. Although functionally related to other NNRTIs, capravirine is structurally distinct. Capravirine forms an extensive hydrogen-bond network with the reverse-transcriptase main chain, a network that is unlikely to be disrupted by simple side-chain mutations [74]. In preclinical studies, capravirine potently inhibited the reverse transcriptase of several clinical isolates and demonstrated a 10 to 100 fold greater potency than that of nevirapine and delavirdine [75]. Capravirine has a 50% effective concentration (EC_{50}) in the nanomolar or subnanomolar range and maintains activity towards HIV-1 strains harbouring commonly encountered mutations, including L100I, Y181C, and V106A. Importantly, in laboratory studies, capravirine maintains potent activity towards strains with the K103N mutation, which confers high-level resistance to all approved NNRTIs. It appears that reverse transcriptase must undergo double or triple mutations to acquire high-level capravirine resistance, which promises to delay the appearance of capravirine-resistant variants.

Capravirine is metabolised by the cytochrome P450 enzyme CYP3A4. In healthy volunteers, capravirine and lopinavir in combination were assessed: lopinavir concentrations were reduced by 40% and capravirine plasma concentrations increased by 5-fold [76] .

In 2001, trails assessing capravirine were suspended for over a year pending safety investigations by the FDA, followin g reports of vasculitis in dogs. No reports of vasculitis in humans have been observed and clinical trials have now been recommenced.

A phase II study in which NNRTI-experienced individuals with viral load rebound were randomised to receive one of two doses of capravirine (2100 or 1400 mg daily) or placebo plus nelfinavir and two new nucleoside reverse transcriptase inhibitors (NRTIs) found that 50% of the capravirine group had viral load below 400 copies/mL after 16 weeks [77]. The median HIV RNA viral load reduction in the 2100 mg group fell by 1.5 log, compared with 2 log in the 1400mg group. However, there was no significant difference in the number of viral load rebounds between the placebo and capravirine groups in this study, and the 1400mg group generally performed better than the 2100mg group, driven by a higher rate of adverse events at the higher dose (nausea, vomiting and diarrhoea). No cases of rash were described. Consequently, the 1400mg dose has now been selected for further development. Sixteen of 36 patients in this study who chose to continue taking capravirine after the study was suspended still had undetectable viral load after 39 to 49 months of therapy. Among patients with detectable viraemia, 70% remained susceptible to capravirine despite high-level resistance to efavirenz and nevirapine.

Capravirine is currently being tested in two international studies, one in antiretroviral-naïve individuals and a further study in combination with lopinavir/r and a NRTI backbone in individuals failing an NNRTI regimen.

TMC-125 (Etravirine)

TMC-125, a new, next generation NNRTI and one of the most exciting drugs in development, has a diarylpyrimidine-based structure that interferes directly with the global hinge-bending mechanism that controls the co-operative motions of the transcriptase subdomains (Fig. **1**). However, the molecular flexibility of the diarylpyrimidine structure allows TMC-125 to accommodate efficiently mutational changes in the binding pocket even in the presence of significant mutations [78]. TMC-125 has an EC_{50} of 1.4 nM and an EC_{90} of 2.9 nM against wild-type HIV. It has demonstrated extensive *in vitro* activity against both wild-type and NNRTI-resistant HIV strains.

In antiretroviral naïve individuals, TMC-125 as monotherapy has produced a decrease in HIV RNA of 2 log copies/mL. In a short-term proof-of-concept study, sixteen individuals receiving an NNRTI-containing antiretroviral regimen (thee on efavirenz and thirteen on nevirapine) with

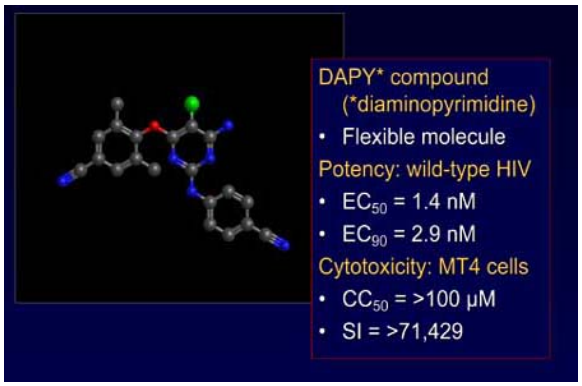
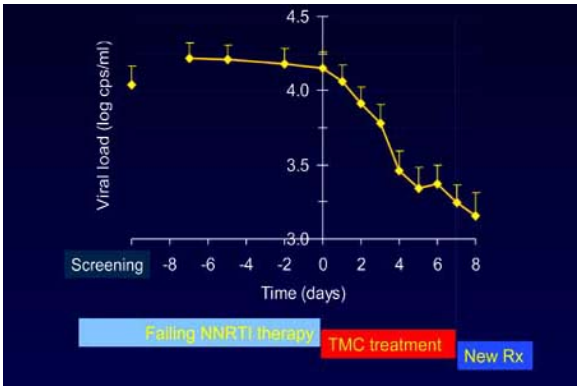


Fig. (1). The structure of TMC125.

an HIV-1 RNA viral load of > 2000 copies/mL and phenotypic resistance to NNRTI, received TMC-125 for 7 days, as a substitute for their current NNRTI in their failing therapy [79]. A median decrease of 0.89 log HIV RNA copies/mL was seen after 8 days of treatment (Fig. **2A** and Fig. **2B**). On average, patients had two NNRTI-associated mutations present. The most frequently reported adverse events were diarrhoea (31.3%) and headache (25%); no rashes were seen. A long-term phase IIb dose finding study (TMC125-C203) in treatment-experienced patients is currently recruiting HIV-1 infected subjects in a number of countries in Europe and in Canada.



	TMC125 (N=16)
Mean (SE) change in viral load at day 8 (log)	-0.86 (0.13)
Median change in viral load at day 8 (log)	-0.89
VL decrease > 0.3 log in 1 week	88% (n=14)
VL decrease > 0.5 log in 1 week	75% (n=12)
VL decrease of >1 log in 1 week	**44% (n=7)**

Fig. (2). As per the figure label.

PROTEASE INHIBITORS

Tipranavir

Tipranavir (TPV) is the first of a new class of non-peptidic protease inhibitors. It is highly selective for the HIV protease enzyme and demonstrates potent *in vitro* activity against wild-type HIV-1 and HIV-2. Against clinical HIV isolates, the TPV EC_{90} was 0.1 µM and in the presence of a mixture of 75% human serum and 10% foetal bovine serum 1.4 µM [80]. TPVs activity against PI-resistant strains results from its molecular flexibility. The molecule has the ability to fit into the active pocket of the protease enzyme in viruses that have become resistant to other PIs [81].

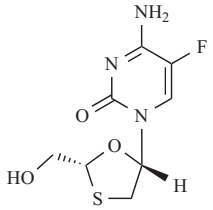


Fig. (3). As per the figure label.

In an *in vitro* study, 105 HIV isolates were taken from patients who were heavily PI experienced; the majority of these isolates was broadly cross-resistant to PIs with more than a 10-fold phenotypic resistance to three or four of the currently available PIs. There was an average of 6.1 Pr gene mutations per isolate. 95 isolates (90%) showed phenotypic susceptibility to TPV, eight showed 4- to 10- fold reduced susceptibility and only two isolates had more than 10-fold resistance to TPV.

TPV is metabolised by the cytochrome P450 3A4 (CYP3A4) iso-enzyme group. Plasma levels of TPV are markedly enhanced in the presence of ritonavir (RTV) boosting. The target through plasma concentration of TPV is 20 µM, a value that is 10-fold higher than the IC_{90} for HIV strains that are resistant to currently available PIs. In health volunteers, co-administration of TPV and RTV were studied and all co-administered doses apart from 250 mg TPV / 200 mg RTV twice daily achieved plasma concentrations above the 20 µM target [82].

The RESIST-1 and -2 studies (Randomised Evaluation of Strategic Intervention in Multi-Drug Resistant Patients with Tipranavir) are two large studies assessing TPV versus a comparator PI (CPI) with optimised background in the US and Europe, respectively. Interim 24 week results from these studies have recently been presented [83, 84]. Both studies evaluated RTV-boosted TPV (500mg TPV / 200 mg RTV twice daily) in comparison to other boosted PIs with the same design: enrolling patients who had failed all three drug classes including two PIs, patients with at least one primary Pr mutation but no more than two of the significant mutations at 33, 82, 84 and 90 and at study entry have an HIV RNA of at least 1000 copies/mL on a PI-containing regimen. Based on genotypic resistance testing, a background regimen was designed prior to randomisation to either TPV or a comparator RTV-boosted PI.

In the RESIST-2 study, a total of 863 patients were enrolled, with a median baseline CD4+ cell count of 185 cells/mL and HIV RNA of 4.77 $\log_{10}$ copies/mL. Among those in the comparator arm, approximately 39% were placed on a regimen containing amprenavir/ritonavir or lopinavir/ritonavir. 11.5% had enfuvirtide included in their regimen, which is significantly fewer than in RESIST 1.

At 24 weeks, in an intent-to-test analysis, 41% of patients on a TPV-based regimen had a viral load decline of at least 1 log copies/mL compared with only 14.9% on the CPI arm. Furthermore, for those on TPV, 33.6% reached an HIV RNA <400 copies/mL versus 13.1% and 22.5% versus 8.6% an HIV RNA <50 copies/mL respectively. For those also treated with enfuvirtide, 38.5% versus 13% had an HIV RNA <400 copies/mL CD4+ lymphocyte cells increased by 31 cells/mL in the TPV arm versus only 1 cell/mL. During the first 8 weeks, discontinuation rates were similar in both arms. Clinical adverse events and lab abnormalities were similar in the two arms, although more patients on tipranavir had grade 3 or 4 elevations of cholesterol, triglycerides, and liver function tests. Similar results have been reported from the RESIST-1 trial, with a slightly higher number of individuals also treated with enfuvirtide.

These promising clinical results highlight the importance of using one new active agent with a further second active agent such as enfuvirtide. Combining TPV with other another active PI may also be an attractive treatment option in highly-experienced patients. However, results from a 24-week, open label safety and pharmacokinetic study of TPV/RTV (500/200 mg twice daily) alone or in combination with a second boosted PI (amprenavir, lopinavir or saquinavir) in 315 highly treatment-experienced patients were recently described. In this study, the co-administration of TPV/RTV was associated with a substantial reduction in the area-under-the-curve of the other compounds: 70% reduction in saquinavir; 45% reduction in amprenavir; and 49% reduction in lopinavir. These results cast doubt on the possibility of co-administering tipranavir with other protease inhibitors, even when boosted with 200 mg of ritonavir twice daily.

TMC-114

TMC-114 is an investigational nonpeptidic PI with *in vitro* activity against viral isolates, some of which had high-level resistance to all currently available PIs. Some features of the compound are an EC_{50} of 4.6 nM and an EC_{90} of 10 nM for wild type HIV, making it a potent and selective inhibitor, with a selectivity index of >2000. TMC-114 shows no or a slight decrease in potency against highly-PI-cross resistant clinical isolates [85].

In humans, TMC-114 is rapidly absorbed from the GI tract when administered as an oral dose, and *in vitro* studies have demonstrated that TMC-114 is mainly metabolised by CYP3A4 [86]. After repeated dosing of TMC-114 alone, the most frequently reported adverse events in healthy volunteers were maculopapular rash, starting 8-10 days after treatment, and diarrhoea, mostly starting 2-3 days after treatment. Interestingly, in the presence of RTV boosting, the frequency of adverse events appeared to be lower when compared to TMC-114 alone.

In HIV-1 infected individuals, TMC-114/RTV has been evaluated in 50 patients in a phase IIa study (TMC-114-C207) [87]. In this trial, multiple PI-experienced patients currently receiving a failing PI regimen were randomised to a control arm or one of three TMC-114/RTV doses (300/100 mg bid, 600/100 mg bid or 900/100 mg qd) for two weeks. Subjects had a median of three primary PI mutations. Significant reductions in plasma HIV RNA were observed in all three of the TMC-114/RTV arms with an overall reduction of -1.35 log copies/mL compared to +0.02 log copies/mL in the control arm. In addition, approximately 40% of subjects in the TMC-114/RTV groups achieved a plasma HIV RNA <400 copies/mL. The most common adverse events were gastro intestinal and CNS disorders. This study was conducted using a TMC-114 oral solution. A solid formulation has been developed and shown to have a similar pharmacokinetic profile.

Currently, results are awaited from a larger, multi-centred randomised 24 week study comparing TMC-114/RTV with a comparator PI arm (The TMC-114-C213 study). Antiviral activity, safety and tolerability will be assessed in approximately 300 patients assigned to four different dosing regimens of TMC-114/RTV (TMC-114/RTV 400/100 qd, 800/100 qd, 400/100 bid and 600/100 bid).

DISCUSSION

Fewer than one million HIV infected individuals are currently receiving anti retroviral therapy. Present antiretroviral therapy costs between $10,000 and $20,000 per year, which provides excellent value for money in developed countries with a cost of about $10,000 per life year saved; the lives saved are the essentially young, fit and potentially economic productive section of the population. This compares very favourably with many other drugs for chronic therapies in current use. Nevertheless, such drug costs are completely out of the reach of 99% of the population suffering from HIV infection. As such, drug companies have become the focus of much vilification for members of the activist community, who see part of capitalist society making large profits but refusing to reduce costs in the developing world. This is largely ignored by political leaders of the world community who have been heavy on the rhetoric of needing to mobilise resources to treat the HIV pandemic but relatively slow to respond by providing such resources. This may have changed with the recent successful passage of a bill through Congress to provide 15 billion dollars to alleviate HIV in parts of the developed world.

In the earlier years of the epidemic, providing effective and/ or new anti retrovirals to the developing world was thought to be out of question. Unfortunately, in much of the developed world, the prevalence of HIV is so high that the hopelessness engendered by lack of treatment renders prevention messages relatively ineffective.

The pendulum of the public opinion is now swinging towards provisional antiretroviral therapy in resource poor settings; leading figures in this endeavour include the two Bills, Clinton and Gates. Clearly, drug companies have an important role to play with many now prepared to provide drugs at cost to the developing world and to waive intellectual property rights in such countries. That alone will

not be sufficient as the logistics of providing antiretroviral therapy are equally important. Drug companies may have a continuing role to play, as part of public private partnerships where the particular skills of profit making organizations are concentrating on outcomes and methods of delivery may be crucial and relatively inexpensive to share with developing communities. Nevertheless, the developed world can procure and provide the health care infrastructures required in many of these countries. This would have broadly beneficial effects on humanity over and above the more effective treatment of HIV disease.

The limitations of anti retroviral treatment strategies at a physical (suppression of viraemia) and political (widespread availability) level have underscored the need to develop more effective strategies to control the spread and pathogenesis of HIV. In recent years, the demand for new antiviral strategies has increased markedly. There are many contributing factors to this increased demand, including the ever-increasing prevalence of chronic viral infections such as HIV and hepatitis B, as well as the emergence of new viruses such as the SARS coronavirus. The weaknesses of current drugs in the treatment of HIV are being tackled with new drugs that address some of the challenge of improving resistance profiles. Because of their early stage of development, the question of improved tolerance remains largely unanswered for most of these compounds and many such drugs will undoubtedly fall by the wayside, with compounds such as amdoxovir, elvucitabine and alovudine already showing significant toxicity. Overall, however, recent progress with new nucleoside analogues has demonstrated that this class of compounds remains a fertile ground for finding valuable additions to current highly active anti retrovirus therapy.

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