Combined therapy for tuberculosis and HIV-1: the challenge for drug discovery

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Combining drug therapies for dual infection by *Mycobacterium tuberculosis* and HIV-1 is made complex by high pill burdens, shared drug toxicities, drug–drug and drug–disease interactions, immune reconstitution inflammatory syndrome, co-morbid diseases and drug resistance in both bacillus and virus. Recently, novel anti-tubercular and anti-retroviral drugs have bolstered the tuberculosis–HIV drug pipelines and may help ameliorate these difficulties. This review article discusses the reasons for current problems of therapy for dual infection. It also identifies promising agents, which may significantly improve co-therapy and thus diminish the great morbidity and mortality of these two pandemics.

The dual pandemics of tuberculosis (TB) and human immunodeficiency virus-1 (HIV) cause considerable morbidity and mortality. One-third of the world's population is infected with *Mycobacterium tuberculosis* (TB), and almost nine million new cases of TB and approximately two million TB deaths occur annually [1,2]. Worldwide, almost 40 million people were infected with HIV and 2.9 million people died with AIDS in 2006 [3]. In 2000, almost 11 million people were co-infected with HIV and TB [1], the majority of who were in the developing world [4]. These two pandemics fuel each other. TB hastens HIV progression to AIDS by accelerating viral replication [5], whilst HIV increases the risk of TB disease (up to 30% annual risk of TB disease in profoundly immune-suppressed patients in endemic areas) [6]. TB–HIV drug therapy is complicated by high pill burdens, shared drug toxicities, drug–drug and drug–disease interactions and the immune reconstitution inflammatory syndrome. Co-morbid diseases, drug resistance and the treatment of latent TB infection provide additional challenges. This review article describes current therapy for TB and HIV, discusses the problems with current TB–HIV therapy, reviews new drugs on the horizon and proposes areas for future research.

Current therapy for tuberculosis and HIV

TB therapy is a multi-drug regimen given over a long period of time. Single agent TB therapy rapidly gives rise to drug-resistant organisms [7]. Multi-drug treatment needs to be prolonged; possible explanations include: *M. tuberculosis* divides slowly, it is metabolically capable of becoming drug insensitive and/or bacilli may become sequestered [8]. The advent of rifampicin and pyrazinamide allowed highly effective 'short course' TB Regimes—usually a two-month intensive phase with rifampicin (R), isoniazid (H), pyrazinamide (Z) and ethambutol (E), followed by a four-month continuation phase with RH (2RHZE/4RH) [9]. Multi-drug-resistant (MDR)-TB, defined as TB resistant to RH, is treated with less effective agents for up to 18 months after sputum conversion. Treatment is often individualised and regimes may be as long as 24 months. Patient adherence is a major problem with such prolonged treatment regimens. There is an urgent need for shorter, effective TB drug regimens.

Highly active anti-retroviral therapy (HAART or ART) for HIV is a life-long multi-drug regimen. In patients infected with HIV,

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2007.08.001

millions of virions are produced daily, and the reverse transcriptase target mutates rapidly. Hence, initial therapies with single or dual nucleoside reverse transcriptase inhibitors (NRTI) such as zidovudine (AZT) and didanosine (ddI) were only partially effective and rapidly led to viral drug resistance [10]. Effective therapy only became possible when non-nucleoside reverse transcriptase (NNRTI) and viral protease inhibitor (PI) drugs were developed. Combinations of these three drug classes lead to prolonged suppression of HIV replication and ultimately to a degree of immune recovery. Adherence to ART is crucial to successful viral suppression, which is very closely related to immune restoration and survival [11].

Difficulties associated with combining current TB–HIV therapies

Shared drug toxicities

Concomitant therapy for HIV and TB is associated with increased risks of adverse drug effects such as nausea, gastrointestinal tract disturbance, peripheral neuropathy, cutaneous reactions, renal toxicity and potentially fatal liver toxicity [12]. Certain drug combinations are contraindicated (Table 1). These toxicities may necessitate therapy discontinuation, which exacerbates immune suppression and predisposes to other opportunistic infections. Shared drug toxicities also compromise adherence to the treatment regimen leading to suboptimal TB and HIV treatment and increasing the possibility of drug resistance.

Drug interactions

Clinically significant pharmacokinetic drug interactions are common in TB–HIV therapy. Many TB–HIV drugs are substrates of metabolising enzymes and drug transporters that are induced or inhibited by key components of anti-TB and ART regimens.

Rifamycins form the backbone of regimens for drug-susceptible TB because they are highly effective, reduce the duration of therapy and are less likely than other TB drugs to select out resistant strains in multi-drug regimens [13]. However, through its activation of a master transcriptional regulator, the pregnane X receptor (PXR), rifampicin induces the expression of a broad array of enzymes and drug-transporting molecules including cytochrome P450 (CYP) 3A and CYP2C isoenzymes, CYP2D6, CYP2B6 and *p*-glycoprotein, amongst others [14]. Thus, repeated doses of rifampicin result in clinically important reductions in the levels of many drugs, amongst them PIs, NNRTIs, trimethoprim and sulfamethoxazole (the last two co-formulated in co-trimoxazole widely used for prophylaxis in patients with advanced HIV-1 infection) [15,16]. The co-localization of *p*-glycoprotein and CYP enzymes in enterocytes, hepatocytes and renal tubular cells may enhance the effects of rifampicin on common substrates, such as PIs, causing more extensive pre-systemic metabolism and accelerated drug elimination. The clinical consequences of rifampicin-related decreases in serum concentrations of the anti-retroviral drugs have not been fully studied, but they potentially lead to loss of anti-viral efficacy and stepwise accumulation of resistance mutations [17–20]. Whilst NNRTIs, besides delavirdine, can be given with rifampicin [21], dose increase may be necessary. All PIs, except ritonavir-boosted PIs, are contraindicated with rifampicin [22]. Certain ritonavir-boosted PIs can be used with rifampicin, but increased doses of ritonavir or a higher dose of the companion PI are required.

The rifamycin rifapentine has a longer half-life suitable to intermittent administration that might simplify therapy. Whilst rifapentine is also a marginally less potent inducer of CYP than rifampicin it has not been widely introduced as it is associated with increased rates of TB drug resistance when used once weekly during the continuation phase of TB therapy [23]. Intermittent rifampicin therapy in the continuation phase is also associated with rifampicin resistance in patients with advanced HIV infection [24]. Rifabutin, the rifamycin causing least induction of CYP enzymes, is safe to use with most NNRTIs and PIs, except delavirdine and saquinavir. However, it is also a substrate for CYP3A4 [25]. Thus, its serum concentration and toxicity are increased when co-administered with PIs and decreased when co-administered with efavirenz and RFB dose adjustments are required in these settings [15]. Rifabutin and the anti-retroviral nevirapine can be given together at standard doses, but delavirdine is contraindicated with rifabutin [15]. Also, the cost of rifabutin precludes its use in the developing world.

Although they are of lesser importance, other pharmacokinetic interactions may confound combined treatments. Isoniazid is an inhibitor of CYP2C19 and CYP3A, PIs inhibit CYP3A, CYP2D6 and *p*-glycoprotein, and efavirenz and nevirapine induce the expression of CYP3A4 and CYP2B6. Other commonly co-administered drugs also cause important changes in anti-retroviral concentrations through induction or inhibition of CYP isoforms (e.g. anticonvulsants like carbamazepine and phenytoin may decrease, and azole anti-fungals, macrolide antibiotics and H2 antagonists may substantially increase PI or NNRTI concentrations).

Pharmacodynamic interactions further complicate combined treatment of TB and HIV. Unanticipated hepatotoxicity has been reported in healthy volunteers receiving adjusted dose PIs in combination with rifampicin [26,27]. Interestingly, repeated doses of RIF before the introduction of the PIs appear to be associated with a higher risk of hepatotoxicity than the introduction of rifampicin after establishing regular doses of the PIs. Although not adequately studied, such high rates of hepatotoxicity have not been reported in patients receiving increased doses of PIs with rifampicin-based TB regimens, indicating that disease-related modulation of hepatotoxicity can occur.

The effect of HIV infection on the concentrations of orally administered first-line anti-tubercular drugs is also a concern. Whilst currently available studies are not entirely consistent, it appears that HIV-infected patients achieve not only somewhat lower concentrations of rifampicin and ethambutol in particular but also isoniazid and pyrazinamide [28–31]. Patients with more advanced HIV disease and those with diarrhoea appear to be at most risk. Although these concentration reductions do not appear to have a marked effect on treatment outcomes their importance has not been fully evaluated.

High pill burden

Combined therapies for TB and HIV together with the recommended co-trimoxazole prophylaxis lead to a very high pill burden—average of 15 pills daily in South Africa for 6–22 months (fixed dose combinations (FDC) for TB medication but not ART). Furthermore, in high burden countries standard treatment approaches are adopted and FDCs are often used to reduce the pill burden and to simplify drug supply, prescribing and admin-

TABLE 1

Shared drug toxicities in HIV/TB patients

Side-effect	Anti-retrovirals	First-line TB drugs	MDR-TB drugs	Other drugs commonly used in HIV	Other HIV disease
Peripheral neuropathy	**d4T, ddI**	H, E (rare)	**Cy**, Te, FQ, **Et**, Ka, Am, Lin		HIV itself
Hearing loss		S	Ka, Am, Cpr, Clr		
Vertigo		S	Ka, Am, Clr		
Optic neuritis		E, H (rare)	Et (rare), PAS (rare), Lin		
Seizures		H	Cy, Te, Of, Ci [and other FQ – rare]		
Psychosis	EFV	H	Cy, Te, Of, Ci, [other FQ] Et	TMP-SMX, steroids	HIV itself
Depression	**EFV**		**Cy**, **Te**, Of, Ci, Et	TMP-SMX	HIV itself
Nausea & vomiting	AZT, ddI, PI: IDV,amprena-vir (other PIs)	Z, Rfm, H, E	Et, Of, Ci, [other FQ], PAS, Clf, Lin	TMP-SMX, Amphotericin B	OI, IRIS
Gastritis		E, Z	Et		
Transaminitis	**NVP**, **PI**, EFZ	Z, **R**, H	Of, Ci [other FQ], Et, Cy, Te, PAS, Clr	TMP-SMX, Azoles	OI
Hepatic steatosis	d4T				OI, IRIS
Cholestasis		R	Clr	TMP-SMX	AIDS cholangiopathy
Nephrotoxicity	TDF (including Fanconi syndrome)	**S**, R (interstitial nephritis & GN), Z+H also rarely cause interstitial nephritis	**Ka, Am, Cpr**, FQ – rarely cause IN, PAS causes crystalluria	**Amphotericin B**, TMP-SMX (interstitial nephritis)	HIVAN
Hypokalaemia	TDF		Ka, Am, Cpr	Amphotericin B	
Renal calculi	IDV			TMP-SMX	
Arthralgias and gout		**E, Z**, H, R	Of, Ci, [other FQ, PAS]	**Thiazide** (gout)	HIV itself
SJS/TEN	NNRTIs	R, H (both rarely)	Thiacetazone, Clr, PAS, FQ	TMP-SMX	
Skin rash	NNRTIs, ABC, PI	Z, R, H, S, E	FQ, Clf, PAS, Clr, Cpr, Et, Cy, Te	TMP-SMX	Folliculitis & asteatosis
Hypersensitivity	ABC	R, S		TMP-SMX	
Leucopenia, anaemia	**AZT**, 3TC	R, H, Z (sideroblastic anaemia), RHZE rarely cause thrombocytopenia	FQ, strep, Cy (megaloblastic), PAS, Lin, Cpr, Clr (last 4 also thrombocytopenia)	**Ganciclovir**, TMP-SMX, Amphotericin B	HIV itself
Lactic acidosis	d4T, ddI, AZT		Lin		
Pancreatitis	ddI, d4T	H	Lin, Clr	TMP-SMX	
Insulin resistance	PI esp IDV			steroids	
Hyperlipidaemia	PI (except ATV), d4T			steroids	
Lipoatrophy	d4T				
Lipodystrophy	PIs				
Hep B flare if drug discontinued	TDF, FTC, 3TC				
Teratogenic	EFV	S	Et	steroids	
Osteoporosis	TDF			steroids	

Antiretrovirals D4T = stavudine, ddI = didanosine, Efv = efavirenz, AZT = zidovudine, IDV = indinavir, PI = Protease inhibitor, NVP = nevirapine, TDF = tenofovir, NNRTI = Efv + NVP, ABC = abacavir APV. **First-line TB drugs** Rfm = rifamycins, R = rifampicin, H = isoniazid, E = ethambutol, Z = pyrazinamide, S = streptomycin. **MDR-TB drugs** Cy = cycloserine, Te = Terizidone, Of = Ofloxacin, Ci = Ciprofloxacin, Et = Ethionamide[+prothionamide], Ka = Kanamycin, Am = Amikacin, FQ = fluoroquinolones, Lin = linezolid, Cpr = capreomycin, Clr = clarithromycin, Clf = clofazimine, PAS = p-amino-salicylate. TMP-SMX = trimethoprim sulfamethoxazole, IRIS = immune reconstitution inflammatory syndrome, OI = opportunistic infections. Drugs in boldface should not be used simultaneously because they potentiate the drug side-effect or are associated with significantly increased morbidity or mortality.

istration. Pharmacokinetic interactions necessitating dose adjustment of individual drug components complicate treatment delivery in the setting of programmes reliant on standardised approaches using FDCs. Thus, optimisation of therapy inevitably leads to a greater pill burden.

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome (IRIS), which is due to dysregulated immune recovery [32], occurs in severely immune-suppressed HIV patients typically one to four weeks after ART initiation [33,34]. In tuberculosis-related IRIS an exuberant inflammatory reaction is directed towards mycobacterial antigens [35], resulting in worsening pulmonary infiltrates, pleural effusions, lymphadenitis and potentially fatal neurological tuberculomata [33,34]. Risk factors for TB–IRIS include low baseline CD4 count, high baseline viral load, short duration between TB and ART initiation and disseminated tuberculosis [33,36]. Determining the optimal time to initiate ART in severely immune-suppressed TB patients is difficult [12,25]. Whilst early initiation of ART may increase the risk of TB–IRIS, non-adherence, drug toxicities and drug interactions, the risk of death, other opportunistic infections (OIs) and malignancies may be greater if ART initiation is delayed [37]. Corticosteroid treatment of TB–IRIS is sometimes recommended, but such immunosuppressive therapy may be associated with reactivation of occult OIs and malignancies, such as CMV and Kaposi's sarcoma. A randomised trial of corticosteroids against placebo for TB–IRIS would help resolve this issue.

Co-morbid diseases

HIV-induced immunosuppression, predisposing to OIs and malignancies, coupled with TB–HIV drug side effects and TB–IRIS can give rise to multiple pathologies in certain organs, especially the liver (Table 2). When faced with significant biochemical or clinical evidence of hepatitis it is a dilemma whether to withdraw all drugs or the most likely offending candidates. Evidence certainly suggests withdrawal of rifampicin, isoniazid, pyrazinamide and NNRTI medications, the latter under the cover of a two NRTI 'tail' to reduce the risk of NNRTI resistance. Substituting 'liver friendly' alternatives such as streptomycin and quinolones to continue the treatment of TB is of uncertain efficacy. Investigating these differential diagnoses without the use of invasive techniques such as endoscopic retrograde cholangio-pancreatography or biopsy poses major challenges to clinicians in resource-limited settings. A further problem on resolution of the hepatitis is when and how drugs should be re-introduced. No attempt to re-introduce nevirapine therapy should be made after significant drug-induced toxicity, but it is common experience that anti-TB drugs may all be re-introduced. This is usually done sequentially with monitoring of clinical signs and hepatic enzymes but is a prolonged empirical exercise that maintains the patient in expensive hospital care and at risk of nosocomial infection. Well-conducted clinicopathological studies of adequate numbers of patients are required to address these issues and inform practice.

Drug-resistant HIV

The prevalence of multi-drug-resistant HIV is increasing [38]. This may be accounted for, partly, by the transmission of HIV-1 from drug-experienced to uninfected individuals [39]. Whilst drug resistance (DR) is not associated with increased virulence [40], DR is the leading cause of treatment failure amongst patients infected with HIV [41]. High adherence (>95%) to ART reduces viral replication, which limits the emergence of drug-resistance mutations [42]. Intermediate ART adherence (70–90%) and ART monotherapy or dual therapy increase the incidence of DR [11]. Recent data suggest that moderate adherence to NNRTIs leads to sustained viral suppression [11]. Certain reverse transcriptase mutations conferring resistance to NRTI (K65R, M184V) are associated with reduced viral fitness [43], whilst mutations conferring NNRTI resistance are usually neutral. Interestingly, NNRTI hypersusceptibility is more common amongst viruses from NRTI experienced/NNRTI-naïve patients compared with viruses from NRTI/NNRTI-naïve patients, suggesting that mutations in NRTI-resistant viruses confer structural conformational advantages for NNRTIs at the NNRTI-binding site [44]. Reduced viral fitness of DR HIV-1

TABLE 2

Causes of liver disease in TB–HIV patients

	Drugs	Infections	Malignancies
Transaminitis (ALT >3 times normal)			
	TB drugs: Rif, INH, Z ART: NNRTI, PI Azoles TMP-SMX	Viral Hepatitis A, B, C CMV EBV	
Canalicular pattern (ALP >3 times normal)			
Infiltration	NRTI (steatosis)	Granulomatous hepatitis TB/Mycobacterium avium-intracellulare/TB–IRIS Fungal CMV	Kaposi's sarcoma Lymphoma
Cholangiopathy (USS liver/ERCP)	Rif TMP-SMX	CMV *Salmonella*, *Campylobacter*, *Isospora belli*, *Microsporidium*, *Cryptosporidium*	
Enzyme induction	Macrolides		

- Certain protease inhibitors (atazanavir and indinavir) can cause unconjugated hyperbilirubinaemia
- Sepsis causes transaminitis with conjugated hyperbilirubinaemia
- If non-specific hepatitis (ALT <3 times normal) then consider malnutrition, NRTIs, ethanol, herbal medication and viral hepatitis serology

strains allows their growth to be exceeded by wild-type HIV strains [45]. The detection of DR HIV-1 in ART-naïve patients may consequently be difficult, as standard population-based genotyping methods only detect viral populations that are greater than 20% of the total HIV-1 population [45]; drug pressure allows the subsequent detection of DR strains [38]. In addition, DR is increased when a failing ART regimen is maintained (even though stable levels of CD4 and VL are preserved over time) and may limit future treatment options [46,47]. New HIV drugs are thus required to overcome cross-resistance and offer alternative therapy in treatment failure.

Drug-resistant tuberculosis

The continued emergence of drug-resistant TB [48] may be due to several factors: poor directly observed treatment short course (DOTS) implementation, the possible greater biological propensity of some strains of TB to become drug resistant (e.g. W-Beijing [49]) and HIV co-infection that is likely to be associated with greater bacterial burdens. W-Beijing strains of TB have been associated with HIV and a greater propensity to become drug resistant. Biologically these strains are postulated to interact in an immune subverting manner because they produce an immunosuppressive phenolic glycolipid [50]. National DOTS programmes require substantial infrastructure and political commitment, which are often suboptimal in the developing world. TB–HIV co-infection is also associated with significantly reduced RIF drug levels, which may allow the selection of drug-resistant TB bacilli [28,30]. Patients receiving MDR-TB treatment may also be at risk of extensively drug-resistant (XDR) TB (defined as MDR plus resistant to at least a quinolone and a second line injectable drug [51,52]) as current MDR-TB therapy is prolonged, poorly tolerated and less effective than first-line TB therapy. Worryingly, the nosocomial acquisition of XDR-TB has recently been documented [53]. Rapid diagnostic methods to ascertain drug resistance and correct infrastructure augmented by a substantial financial commitment by both first and third world countries will be required to combat the expanding TB pandemic and prevent the spread of drug-resistant TB [13].

Treatment of HIV-1-associated latent tuberculosis infection

ART reduces the incidence of TB, though it remains to be seen whether this benefit may be offset by increased survival and an overall increase in lifetime risk. Treatment of latent TB infection (LTBI) also reduces the risk of subsequent TB disease even in HIV-infected people, though the duration of protection is relatively short [54]. It therefore appears logical to potentially combine therapies to prevent TB. However, the risk benefit of preventive TB therapy in these circumstances is unknown: There are significant overlapping hepatic and neurological toxicities as outlined above. In addition, the most effective preventive therapy is isoniazid monotherapy, but this may be associated with an increased risk of isoniazid resistance if inadvertently given to patients with active disease [55]. Therefore, whilst the prescribing of either isoniazid or ART has significant benefits in HIV-infected persons, a randomised controlled trial is still needed to determine the efficacy and risks of combination isoniazid/ART therapy. The combination regimen of rifampicin and pyrazinamide for two months was associated with liver toxicity especially in HIV-uninfected persons and is no longer recommended [56]. There is very little evidence to guide prescription of preventive therapies in persons exposed to MDR-TB [57].

Drugs on the horizon

In order to meet the challenges of TB–HIV co-infection, new TB and HIV drugs are urgently needed. These new TB drugs should shorten the duration of TB therapy or significantly reduce the number of doses under DOTS, have efficacy against both drug-susceptible and MDR-TB, be effective in treating LTBI, have a new site of drug action thus limiting cross-resistance and not be metabolised by CYP or induce or inhibit CYP, thus limiting shared toxicities between HIV and TB therapy. Since 2000, several novel TB and HIV drug candidates have been identified (Tables 3 and 4 [58,59]).

TB drugs in development

PA-824

PA-824 is a nitroimidazo-oxazine. It requires activation by *M. tuberculosis* F420 factor and inhibits synthesis of cell wall lipids as well as protein synthesis. The TB alliance is currently conducting phase 1 clinical trials of PA-824 [60]. Preliminary studies suggest that PA-824 will be active against MDR-TB and has no cross-resistance with other anti-tubercular drugs. Importantly, it is not metabolised by CYP and does not induce or inhibit CYP. It had similar bacteriostatic efficacy to rifampicin and was more efficient than isoniazid or moxifloxacin but less efficient than rifampicin

TABLE 3

TB–HIV drugs in development

TB	HIV
Novel chemical entities	**Attachment inhibitors**
ATP synthase inhibitor:	Dextran sulfate
R 207910/diarylquinolineTMC 207	Heparin
FAS20013	Cyanovirin-N
Cell wall inhibitors:	Cyclotriazadisulfonamide analogues
Nitroimidazo-oxazine PA-824	PRO 2000
Nitroimidazo-oxazole OPC-67683	TNX 355
Dipiperidine SQ-609	PRO 542
Translocase I inhibitor	BMS 806
InhA inhibitors	**Co-receptor binding inhibitors**
Isocitrate lyase inhibitors	CCR5: SCH-D
Protein synthesis inhibitor	Maraviroc
Pyrrole LL-3858	Aplaviroc
Other: Pleuoromutilins	TAK 779
	Ancriviroc
	CXCR4: AMD 070
Based on existing chemical entities	Plerixafor
Fluoroquinolones	**Fusion inhibitors**
Moxifloxacin	Tifuvirtide
Gatifloxacin	
New quinolones	
Non-fluorinated quinolones	**Non-nucleoside reverse transcriptase inhibitors**
Ethambutol derivative:	Etravirine
SQ-109	**Integrase inhibitors**
Macrolides	L 731988
Thiolactomycin analogues	L 870810
Nitrofuranylamines	L 870812
Rifamycin derivatives:	**Maturation inhibitors**
Rifalazil	PA 457
Oxazolidinones:	**Protease inhibitors**
Linezolid	Darunavir

and isoniazid in continuation phase therapy in the mouse model [58,61,62].

OPC-67683

OPC-67683 is a nitroimidazo-oxazole that is similar in structure to PA-824. It inhibits cell wall biosynthesis. Otsuka Pharmaceuticals (Japan) are currently conducting phase 2 clinical trials [60]. Preclinical studies in rodents and dogs suggest that OPC-67683 could be used in HIV/AIDS as it has no effect on CYP. It may have treatment-shortening potential as it synergises *in vitro* with rifampicin and pyrazinamide. OPC-67683 is effective against MDR-TB *in vitro* and displayed no cross-resistance to first line TB therapy. It also has potential to treat LTBI [58,63].

R207910

R207910 is a diarylquinoline and is also known as Compound J and TMC207. It inhibits ATP synthase (AtpE) leading to ATP depletion and pH imbalance [64,65]. It was initially identified by Johnson & Johnson and subsequently developed by the subsidiary Tibotec Pharmaceuticals Limited, where it is undergoing phase 2a clinical trials in both drug sensitive and resistant disease [60]. Murine studies suggest that R207910 has a good safety and tolerability profile and potent early bactericidal activity, matching isoniazid. It had a synergistic effect with pyrazinamide for MDR-TB; R207910/H/Z or R207910/R/Z combinations were more effective than amikacin/Z/moxifloxacin/ethionamide regimens. R207910 displayed no cross-resistance to other TB drugs as it has a novel site of action. It also has the potential to shorten duration of TB therapy. Its drawback is its metabolism by CYP, which will necessitate dose-adjustment if administered simultaneously with rifampicin [58,64,65].

Gatifloxacin

Gatifloxacin is a fluoroquinolone that inhibits DNA gyrase, thus inhibiting TB DNA replication and transcription. Its sponsors and co-ordinators include the OFLOTUB Consortium, the European Commission, WHO TDR and Lupin Ltd. Gatifloxacin is currently undergoing phase 3 clinical trials [60]. Gatifloxacin holds the potential to be the first TB agent to reduce pulmonary TB therapy to four-month duration. There are weak data to support its efficacy against MDR-TB [58,66]. However, there have been concerns about dysglycaemia with gatifloxacin [67].

Moxifloxacin

Moxifloxacin is also a fluoroquinolone and has a similar mechanism of action to gatifloxacin. It is undergoing phase 2 and 3 clinical trials by CDC TBTC, Johns Hopkins University and UK MRC. The TB alliance and Bayer are jointly pursuing clinical development for tuberculosis. Moxifloxacin kills rifampicin-tolerant persisters *in vitro*, and it may help treat MDRTB if co-administerd with ethionamide. Data from the mouse model support the possibility that moxifloxacin when substituted for isoniazid or ethambutol in standard, first-line TB treatment will increase the two-month sputum conversion rate and potentially shorten overall time to stable cure. It may thus shorten duration of TB therapy [58,62,66,68].

SQ-109

SQ-109 is an ethylenediamine and is derived from ethambutol. It is postulated to inhibit cell wall biosynthesis and has intracellular targets, which have not yet been elucidated. Sequella Inc. (in collaboration with the National Institutes for Health) is currently conducting phase 1 clinical trials [60]. Current data suggest that SQ-109 is effective against drug-resistant strains (including ethambutol-resistant strains). SQ-109 appears to be synergistic with isoniazid and rifampicin [58,69].

Pyrrole LL3858

Limited data are available regarding pyrrole LL3858. It is currently undergoing phase 1 clinical trials by Lupin Limited (India) [58]. Available data suggest that LL3858 has potency against standard and drug-sensitive TB strains *in vitro* [58,70].

HIV drugs in development

Second generation agents

Etravirine (TMC125)

Etravirine, also known as TMC-125, is a next-generation NNRTI. It is a highly flexible, di-aryl-pyrimidine (DAPY) compound that enables favourable binding interactions with mutant HIV strains as well as wild-type virus [71]. It is being developed by Tibotec (Johnson & Johnson) and is currently in phase 3 clinical trials and may become the first NNRTI suitable for use in NNRTI-experienced patients [71,72].

Darunavir (TMC 114)

Darunavir is a second generation PI that is administered with low dose ritonavir. It is relatively resistant to mutations that confer PI resistance and is in phase 3 trials in naïve-experienced patients and ART-experienced patients [73].

New class agents

CCR5 inhibitors

Maraviroc

Maraviroc, also known as UK-427 and 857, is a CCR5 antagonist. It blocks the CCR5 co-receptor on CD4 cells preventing HIV that uses this receptor from entering CD4 cells. It is manufactured by Pfizer and was approved for use by FDA on 24 April 2007. Furthermore, it was granted accelerated approval on 6 August 2007 for combination anti-retroviral treatment of adults infected only with detectable CCR5-tropic HIV-1, who have evidence of viral replication and who have HIV-1 strains resistant to multiple anti-retroviral agents [74]. Maraviroc is a substrate for CYP3A4 so has potential interactions with rifampicin, NNRTIs and PIs; levels of maraviroc are increased in patients also taking atazanavir, ritonavir-boosted lopinavir (Kaletra) and ritonavir-boosted saquinavir (Invirase) [59].

Vicriviroc (SCH-D) and aplaviroc (GSK-873140)

Vicriviroc is also a CCR5 antagonist and has a similar mechanism of action to maraviroc. It is being developed by Schering-Plough and is currently undergoing phase 2 clinical trials in treatment-experienced patients. Vicriviroc was discontinued in treatment-naïve patients because of poor virological outcomes. In one study, five patients in the vicriviroc arm developed malignancies, but the Drug and Safety Monitoring Board could not determine a causal link so the study was continued [59]. Phase 3 trials of GlaxoSmithKline's CCR5 antagonist, aplaviroc, were stopped in October 2005 following reports of severe liver toxicity [75].

TABLE 4

Potential benefits, toxicities and metabolism of new TB–HIV drugs in development

Drug name	Potential benefits	Potential for treating LTBI	Potential for shortening TB therapy	Metabolism and effect on CYP	Potential toxicities	Other
B drugs in development						
PA-824	Bacterio-cidal and bacterio-static, novel target reducing potential cross-resistance with existing drugs, treats MDR-TB	Yes	Unknown	No CYP metabolism		Requires activation by mTB F420 factor (Rv3547 enzyme)
OPC-67683	Novel target reducing potential cross-resistance with existing drugs, high MTB specificity, Treats MDR-TB	Yes	Yes	No CYP metabolism		Intracellular activity. Requires activation by Rv3547 enzyme
TMC 207/R207910	Novel target reducing potential cross-resistance with existing drugs, Bacterio-cidal and bacterio-static, Treats MDR-TB	Yes	Yes	Yes, CYP3A4		Synergistic with other TB meds esp. PZA
Moxifloxacin	Treats MDR-TB	Yes	Yes	Ciprofloxacin inhibits hepatic microsomal enzymes	GIT, hypersensitivity, CNS, hepatic necrosis, interstitial nephritis	Cross-resistance amongst quinolones
Gatifloxacin	Treats MDR-TB (weak data)		Yes	Ciprofloxacin inhibits hepatic microsomal enzymes	As above, dysglycaemia	Cross-resistance amongst quinolones
SQ-109	May treat ethambutol-resistant strains			CYP2D6 CYP2C19		

Drug name	Potential benefits	CYP metabolism/effect	Potential toxicities	Other
HIV drugs in development				
Etravirine	Inhibits replication of wild-type and drug-resistant HIV		No safety concerns in phase 2 trials	
Darunavir	Retains efficacy against multi-PI-resistant viruses, higher genetic barrier to resistance	Metabolised by CYP		
Maraviroc	Active against diverse HIV-1 isolates from different clades, Does not compete with chemokine binding	Yes, substrate for CYP3A4	Mild/moderate Headache, dizziness, asthenia, flatulence, rhinitis	Immune modulation, escape mutants, altered viral tropism
Aplaviroc	Trials discontinued	Yes, substrate for CYP3A4	Liver toxicity	
Vicriviroc	May be beneficial in salvage therapy—awaiting study conclusion		Poor virological outcomes in naïve patients	
Raltegravir	Virological benefit in salvage therapy	No (metabolised by glucuronidation)	Similar to placebo	Potential interaction with antibiotics
Elvitegravir	Efficacy against MDR-HIV	Metabolised by CYP and glucuronidation, induces CYP3A	Similar to placebo	Potential interaction with antibiotics

Integrase inhibitors: raltegravir and elvitegravir

Raltegravir, also known as MK-0518, is an integrase inhibitor and inhibits HIV–DNA integration into host DNA. It is being developed by Merck and is undergoing phase 3 clinical trials. Raltegravir's safety profile is comparable to placebo, and it has demonstrated virological benefit in salvage ART [76]. It is metabolised by glucuronidation (UGT1A1) and has no significant effect on CYP3A4 [59,76,77]. Elvitegravir, known as Gilead-9137, is also an integrase inhibitor and has a similar mechanism of action to raltegravir. Elvitegravir demonstrates efficacy against multi-drug-resistant HIV and has a side effect profile similar to placebo. It is metabolised by glucuronidation and CYP, so it has important drug interactions. It is also an inducer of CYP3A4. In clinical studies it is being used with ritonavir boosting to increase its half-life from three to nine hours, increase its AUC and prevent auto-induction of its metabolism [59,77,78].

Maturation inhibitor: PA-457

PA-457, also known as DSB, is a maturation inhibitor and blocks HIV maturation by disrupting cleavage of the capsid precursor. Panacos Pharmaceuticals is currently conducting phase 2 clinical trials. Data on the metabolism and potential toxicity of PA-457 are limited [59,79].

Future areas of research

Insight into how *M. tuberculosis* persists may illuminate novel ways to reduce the prolonged duration of TB therapy and emergence of drug resistance. In particular, there has been a recent advance in determining the bacillary determinants involved in adaptation to hypoxia: A state thought to be important in latent lesions [80]. It is also increasingly clear that metabolic adaptation to persistence involves a switch in metabolism to the use of fatty acids as a source of carbon. Deletion of both genes encoding isocitrate lyases 1 and 2 impairs the persistence of TB [81]. The absence of these gene products in humans may facilitate the development of glyoxylate cycle inhibitors as new drugs for the treatment of tuberculosis [81].

Given that novel anti-tuberculosis and anti-retroviral agents will be used concurrently in the future, structure–activity and structure–toxicity analyses combined with medicinal chemistry may address drug interactions at the design phase. *In vitro* screening systems for drug interactions with CYP enzymes and drug transporters are in use [82,83]. *In silico* prediction of adverse effects triggered by drugs metabolised by cytochrome P450 3A4 (metabolic transformations, drug–drug interactions) has been reported and may become more widespread at the discovery phase [84]. The clinical relevance of drug–drug interactions is best assessed in relevant patient populations. Population-based methods can be used during phases 2 and 3 of clinical drug development and in post-marketing evaluation to quantify known pharmacokinetic interactions and detect unanticipated interactions [85].

Conclusions

With the aid of philanthropic organisations, pharmaceutical companies and the TB alliance, numerous TB and HIV drugs with novel sites of action are currently in the drug development pipeline. Whilst phase 3 clinical trials still have to be conducted, these novel drugs hold the promise of improving combined TB–HIV therapy with the reduction of shared drug toxicities, drug resistance and long duration of TB therapy. It is our hope that these research ventures will impact those most afflicted by HIV and TB. All current labours will be in vain without the combined efforts of garnering political and societal commitment, significantly improving the infrastructure and adherence of DOTS and ART and making these new drugs financially available to the developing world.

Acknowledgements

The authors would like to thank Chelsea Morroni for her helpful comments on the manuscript. The authors are supported by the Wellcome Trust (072070, 081667), MRC (UK), MRC of South Africa, European Union (SANTE/2005/105-061-102) and the Bill and Melinda Gates Foundation (37822).

References

1 Corbett, E.L. *et al.* (2003) The growing burden of tuberculosis; global trends and interactions with the HIV epidemic. *Arch. Intern. Med.*163, 1009–1021
2 WHO, (2006) *Global tuberculosis control: surveillance planning financing*, Geneva WHO/HTM/TB/2006.362
3 UNAIDS, (2007) *The Joint United Nations Programme on HIV/AIDS* http://data.unaids.org/pub/EpiReport/2006/02-Global_Summary_2006_EpiUpdate_eng.pdf [Accessed 29 May 2007]
4 Dye, C. *et al.* (1999) Consensus statement. Global burden of tuberculosis estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA*282, 677–686
5 Collins, K.R. *et al.* (2002) Impact of tuberculosis on HIV-1 replication, diversity, and disease progression. *AIDS Rev.*4, 165–176
6 Wood, R. *et al.* (2000) Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J. Acquir. Immune Defic. Syndr.*23, 75–80
7 Mitchison, D.A. (2005) Drug resistance in tuberculosis. *Eur. Respir. J.*25, 376–379
8 Connolly, L.E. *et al.* (2007) Why is long-term therapy required to cure tuberculosis? *PLoS Med.*4, e120 0001–0008
9 el-Sadr, W.M. *et al.* (1998) Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). *Clin. Infect. Dis.*26, 1148–1158
10 Erice, A. *et al.* (1993) Brief report: primary infection with zidovudine-resistant HIV-1. *N. Engl. J. Med.*328, 1163–1165
11 Nachega, J.B. *et al.* (2007) Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Ann. Intern. Med.*146, 564–573
12 Dean, G.L. *et al.* (2002) Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS*16, 75–83
13 Rattan, A. *et al.* (1998) Multi-drug-resistant *Mycobacterium tuberculosis*: molecular perspectives. *Emerg. Infect. Dis.*4, 195–209
14 Rae, J.M. *et al.* (2001) Rifampicin is a selective, pleiotropic inducer of drug metabolism: studies with cDNA and oligonucleotide expression assays. *J. Pharmacol. Exp. Ther.*299, 849–857
15 CDC, (2007) *Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors* Available from: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm [Accessed 29 May 2007]
16 Ribera, E. *et al.* (2001) Rifampin reduces concentrations of trimethoprim and sulfamethoxazole in serum in Human Immunodeficiency Virus-infected patients. *Antimicrob. Agents Chemother.*45, 3238–3241
17 De Requena, D.G. *et al.* (2005) Nevirapine plasma exposure affects both durability of viral suppression and selection of nevirapine primary resistance mutations in a clinical setting. *Antimicrob. Agents Chemother.*49, 3966–3969
18 Marzolini, C. *et al.* (2001) Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*15, 71–75

19 Dumon, C. *et al.* (2000) Relationship between efficacy, tolerance, and plasma drug concentration of ritonavir in children with advanced HIV-infection. *Ther. Drug Monit.*22, 402–408

20 Masquelier, B. *et al.* (2002) Human Immunodeficiency Virus type 1 genotypic and pharmacokinetic determinants of the virological response to lopinavir-ritonavir-containing therapy in protease inhibitor-experienced patients. *Antimicrob. Agents Chemother.*45, 2926–2932

21 Borin, M.T. *et al.* (1997) Pharmacokinetic study of the interaction between rifampin and delavirdine mesylate. *Clin. Pharmacol. Ther.*61, 544–553

22 Burman, W.J. *et al.* (1999) Therapeutic implications of drug interactions in the treatment of HIV-related tuberculosis. *Clin. Infect. Dis.*28, 419–430

23 Vernon, A. *et al.* (1999) Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. Tuberculosis Trials Consortium. *Lancet*353, 1843–1847

24 Burman, W. *et al.* (2006) Acquired rifamycin resistance with twice-weekly treatment of HIV-related tuberculosis. *Am. J. Respir. Crit. Care Med.*173, 350–356

25 Burman, W.J. *et al.* (2001) Comparative pharmacokinetics and pharmacodynamics of the rifamycin antibacterials. *Clin. Pharmacokinet.*40, 327–341

26 La Porte, C.J.L. *et al.* (2004) Pharmacokinetics of adjusted-dose lopinavir-ritonavir combined with rifampin in healthy volunteers. *Antimicrob. Agents Chemother.*48, 1553–1560

27 Grange, S. *et al.* (2005) Unexpected hepatotoxicity observed in a healthy volunteer study on the effects of multiple dose rifampicin on the steady-state pharmacokinetics of ritonavir-boosted saquinavir and vice versa [abstract no. 35]. *Sixth international workshop on clinical pharmacology of HIV therapy*, Quebec, Canada http://www.hivpresentation.com/assets/85C5CB30-E0C4-D510-0E5E2413A6485A21.PDF [Accessed 13 June 2007]

28 Gurumurthy, P. *et al.* (2004) Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced Human Immunodeficiency Virus disease. *Antimicrob. Agents Chemother.*48, 4473–4475

29 McIlleron, H. *et al.* (2006) Determinants of rifampicin, isoniazid, pyrazinamide and ethambutol pharmacokinetics in a cohort of tuberculosis patients. *Antimicrob. Agents Chemother.*50, 1170–1177

30 Sahai, J. *et al.* (1997) Reduced plasma concentrations of antituberculosis drugs in patients with HIV-infection. *Ann. Intern. Med.*127, 289–293

31 Zhu, M. *et al.* (2004) Pharmacokinetics of ethambutol in children and adults with tuberculosis. *Int. J. Tuberc. Lung Dis.*8, 1360–1367

32 French, M.A. *et al.* (2000) Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med.*1, 107–115

33 Breton, G. *et al.* (2004) Determinants of immune reconstitution inflammatory syndrome in HIV Type 1-Infected patients with tuberculosis after initiation of antiretroviral therapy. *Clin. Infect. Dis.*39, 1709–1712

34 Narita, M. *et al.* (1998) Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am. J. Respir. Crit. Care Med.*158, 157–161

35 Bourgarit, A. *et al.* (2006) Explosion of tuberculin-specific Th1-responses induces immune restoration syndrome in tuberculosis and HIV co-infected patients. *AIDS*20, F1–F7

36 Shelburne, S.A. *et al.* (2005) Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS*19, 399–406

37 Lawn, S.D. *et al.* (2007) Early mortality among patients with HIV-associated TB in Africa: implications for the time to initiate ART [abstract 81]. *Fourteenth conference on retroviruses and opportunistic infections*, Los Angeles http://www.aidsmap.com/en/news/024E25A7-850C-4ED9-A2C3-BB0F852898C3.asp [Accessed 13 June 2007]

38 Turner, D. and Wainberg, M.A. (2006) HIV transmission and primary drug resistance. *AIDS Rev.*8, 17–23

39 Wensing, A.M. *et al.* (2005) Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J. Infect. Dis.*192, 958–966

40 Brenner, B. *et al.* (2002) Persistence and fitness of multidrug-resistant of HIV-1 acquired in primary HIV infection. *J. Virol.*76, 1753–1761

41 Lorenzi, P. *et al.* (1999) Impact of drug resistance mutations on virologic response to salvage therapy. Swiss HIV Cohort Study. *AIDS*13, F17–F21

42 Burman, W.J. (2005) Issues in the management of HIV-related tuberculosis. *Clin. Chest Med.*283–294

43 Turner, D. *et al.* (2004) Diminished representation of HIV-1 variants containing select drug resistance-conferring mutations in primary HIV-1 infection. *JAIDS*37, 1627–1631

44 Whitcomb, J.M. *et al.* (2002) Hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in HIV-1: clinical, phenotypic and genotypic correlates. *AIDS*16, F41–F47

45 Brenner, B. *et al.* (2004) Persistence of multidrug resistance (MDR) transmitted in primary infection leading to one case of superinfection with a second MDR variant. *AIDS*18, 1653–1660

46 Kantor, R. *et al.* (2004) Evolution of resistance to drugs in HIV-1-infected patients failing antiretroviral therapy. *AIDS*18, 1503–1511

47 Cozzi-Lepri, A. *et al.* (2007) Evolution of drug resistance in HIV-infected patients remaining on a virologically failing combination antiretroviral therapy regimen. *AIDS*21, 721–732

48 Shah, N.S. *et al.* (2007) Worldwide emergence of extensively drug-resistant tuberculosis. *Emerg. Infect. Dis.*13, 380–387

49 Rad, M.E. *et al.* (2003) Mutations in putative mutator genes of *Mycobacterium tuberculosis* strains of the W-Beijing family. *Emerg. Infect. Dis.*9, 838–845

50 Reed, M.B. *et al.* (2004) A glycolipid of hypervirulent tuberculosis strains that inhibits the innate immune response. *Nature*431, 84–87

51 Centers for Disease Control and Prevention (2006) Emergence of *Mycobacterium tuberculosis* with extensive resistance to second-line drugs—worldwide, 2000–2004. *MMWR*55, 301–305

52 Centers for Disease Control and Prevention (2006) Extensively drug-resistant tuberculosis (XDR TB)—update. *MMWR* http://www.cdc.gov/tb/xdrtb/update.htm [Accessed 7 August 2007]

53 Gandhi, N.R. *et al.* (2006) Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*368, 1575–1580

54 Woldehanna, S. and Volmink, J. (2004) Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst. Rev.* CD000171

55 de Jong, B.C. *et al.* (2004) Clinical management of tuberculosis in the context of HIV infection. *Annu. Rev. Med.*55, 283–301

56 American Thoracic Society, (2000) Targeted tuberculin skin testing and treatment of latent tuberculosis infection. *MMWR Recomm. Rep.*47, 1–58

57 Jasmer, R.M. *et al.* (2002) Short-course rifampin and pyrazinamide compared with isoniazid for latent tuberculosis infection: a multicenter clinical trial. *Ann. Intern. Med.*137, 640–647

58 Global Alliance for TB drug development. www.accessmed-msf.org/documents/TBPipeline.pdf [Accessed 20 May 2007]

59 Reeves, J.D. and Piefer, A.J. (2005) Emerging drug targets for antiretroviral therapy. *Drugs*65, 1747–1766

60 Ginsberg, A.M. and Spigelman, M. (2007) Challenges in tuberculosis drug research and development. *Nat. Med.*13, 290–294

61 Nuermberger, E. *et al.* (2006) Combination chemotherapy with the nitroimidazopyran PA-824 and first line drugs in a murine model of tuberculosis. *Antimicrob. Agents Chemother.*2621–2625

62 Nuermberger, E. *et al.* (2005) Rifapentine, moxifloxacin, or DNA vaccine improves treatment of latent tuberculosis in a mouse model. *Am. J. Respir. Crit. Care Med.*172, 1452–1456

63 Matsumoto, M. *et al.* (2006) OPC-67683, a nitro-dihydro-imidaooxazole derivative with promising action against tuberculosis *in vitro* and in mice. *PloS Med.*3, 2131–2144

64 Andries, K. *et al.* (2005) A diarylquinoline drug active on the ATP synthase of *Mycobacterium tuberculosis*. *Science*307, 223–227

65 Cole, S.T. and Alzari, P.M. (2005) TB-a new target, a new drug. *Science*307, 214–215

66 Hu, Y. *et al.* (2003) Sterilising activities of fluoroquinolones against rifampin-tolerant populations of *Mycobacterium tuberculosis*. *Antimicrob. Agents Chemother.*47, 653–657

67 Park-Wyllie, L.Y. *et al.* (2006) Outpatient gatifloxacin therapy and dysglycemia in older adults. *N. Engl. J. Med.*354, 1352–1361

68 Burman, W.J. *et al.* (2006) Moxifloxacin versus ethambutol in the first 2 months of treatment for pulmonary tuberculosis. *Am. J. Respir. Crit. Care Med.*174, 331–338

69 Chen, P. *et al.* (2006) Synergistic interactions of SQ109, a new ethylene diamine, with front-line antitubercular drugs *in vitro*. *J. Antimicrob. Chemother.*58, 332–337

70 Ragno, R. *et al.* (2000) Antimycobacterial pyrroles: synthesis, anti-*Mycobacterium tuberculosis* activity and QSAR studies. *Bioorg. Med. Chem.*8, 1423–1432

71 Etravirine: R165335, TMC 125, TMC-125, TMC125. *Drugs R D*7, 367–373

72 Boone, L.R. (2006) Next-generation HIV-1 non-nucleoside reverse transcriptase inhibitors. *Curr. Opin. Investig. Drugs*7, 128–135

73 de Bethune, M.P. and Hertogs, K. (2006) Screening and selecting for optimized antiretroviral drugs: rising to the challenge of drug resistance. *Curr. Med. Res. Opin.*22, 2603–2612

74 http://www.thepinksheetdaily.com/fdcreports/pdly/showPage.do?Page=LoadPRNStory&Story=200707261600PR_NEWS_USPR_____NETH047 [Accessed 7 August 2007]

75 Crabb, C. (2006) GlaxoSmithKline ends aplaviroc trials. *AIDS*20, 21

76 Cooper, D. *et al.* (2007) Results ofBENCHMRK-1, a phase III study evaluating the efficacy and safety of MK-0518, a novel HIV-1 integrase inhibitor, in patients with

triple-class resistant virus. *Program and abstracts of the 14th conference on retroviruses and opportunistic infections [abstract 105a LB]*, Los Angeles, USA, February 25–28 http://www.hivandhepatitis.com/2007icr/croi/docs/030207_a.html [Accessed 14 June 2007]
77 Pommier, Y. *et al.* (2005) Integrase inhibitors to treat HIV/AIDS. *Nat. Rev. Drug Discov.*4, 236–248
78 Mathias, A. *et al.* (2006) Pharmacokinetic characterization of GS-9137, an HIV integrase inhibitor dosed with ritonavir. *Acquir. Immune Defic. Syndr.*43, 1–5
79 Li, F. *et al.* (2006) Determinants of the HIV-1 maturation inhibitor PA-457. *Virology*356, 217–224
80 Voskuil, M.I. *et al.* (2003) Inhibition of respiration by nitric oxide induces a *Mycobacterium tuberculosis* dormancy program. *J. Exp. Med.*198, 705–713
81 Munoz-Elias, E.J. and McKinney, J.D. (2005) *Mycobacterium tuberculosis* isocitrate lyases 1 and 2 are jointly required for *in vivo* growth and virulence. *Nat. Med.*11, 638–644
82 Pelkonen, O. and Raunio, H. (2005) *In vitro* screening of drug metabolism during drug development: can we trust the predictions? *Expert Opin. Drug Metab. Toxicol.*1, 49–59
83 Xia, C.Q. *et al.* (2007) Evaluation of drug-transporter interactions using *in vitro* and *in vivo* models. *Curr. Drug Metab.*8, 341–363
84 Vedani, A. *et al.* (2006) The challenge of predicting drug toxicity *in silico*. *Basic Clin. Pharmacol. Toxicol.*99, 195–208
85 Zhou, H. (2006) Population-based assessments of clinical drug–drug interactions: qualitative indices or qualitative measures. *J. Clin. Pharmacol.*46, 1268–1289