Antiretroviral therapy in developing countries: pharmacologic considerations

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Purpose of review

This article reviews recent studies in the field of clinical pharmacology of antiretroviral drugs and highlights the relevance of the findings to clinical practice in developing countries.

Recent findings

Differences in antiretroviral pharmacokinetics are associated with polymorphisms of genes encoding drug metabolizing enzymes. Inadequate concentrations of antiretrovirals in children are common. A study in African children found subtherapeutic concentrations in 40% of patients receiving efavirenz at recommended doses.

Summary

Recent findings on the pharmacokinetics of antiretroviral agents relevant to clinical practice in developing countries are reviewed. Widespread poverty impacts negatively on HIV/AIDS treatment and prevention efforts. Improved access to treatment, social and economic support and pharmacology research in target populations are needed.

Keywords

anti-HIV agents, developing countries, drug interactions, pharmacokinetics, toxicity

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Introduction

The roll-out of antiretroviral drugs in developing countries has become the largest and most ambitious pharmacology project in history. About 2 million people in developing countries now have access to life-saving antiretrovirals, approximately 28% of those in need [1]. Among treated patients, comparable response rates to those seen in western countries have been demonstrated in the first few years of antiretroviral therapy [2]. It is important to sustain these successes by the efficient use of acceptable, efficacious and minimally toxic regimens. This can be achieved by building up knowledge of the pharmacology of these agents within the context of daily life in resource-limited settings.

Antiretroviral therapy in developing countries

The high disease burden compounded by resource constraints in developing countries necessitates a public health approach to the pharmacology of HIV therapy. While the future of HIV treatment in western countries leans towards individualized medicine [3,4•], the focus in developing countries still remains on the optimization of therapy for large population groups and subgroups living in poverty. Furthermore, guidelines need to be simplified to improve treatment in countries with shortages of skilled health workers and weak infrastructure [5]. As patients and health systems struggle to cope with HIV/AIDS, prevention of new infections must remain a high priority if the Millennium Development Goal of halting and reversing the spread of the pandemic is to be attained.

Developing countries consist of ethnically and environmentally distinct populations. These groups vastly differ from the predominantly male Caucasian participants involved in antiretroviral development studies. Significant variability in antiretroviral drug metabolism can occur due to genetically determined [6,7] differences in hepatic metabolism of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Differences in drug metabolism may also be influenced by factors such as age, sex, diet and nutrition, comorbidities and concomitant medicine use. On account of these differences, a well attended expert panel convened by the Infectious Disease Society of America and the United Nations Programme on HIV/AIDS (UNAIDS) in 2001 called for pharmacokinetic studies to be conducted in the 'neglected populations' living in resource-limited settings [8]. Little progress has been made so far.

A preponderance of fixed-dose combination (FDC) generic agents and a restricted range of drugs, characterise antiretroviral programmes in developing countries. Earlier concerns that generic products were pharmacologically inferior to branded products have been allayed by reassuring

pharmacokinetic data from recent studies [9–12]. The future of the rapid scale-up of mainly generic antiretrovirals in developing countries is, however, uncertain with the implementation of the Trade-Related Aspects of Intellectual Property Rights Agreement (TRIPS), which greatly undermines the ability of developing countries to manufacture their own generic drugs and places them at a disadvantage in price negotiations of imported newer agents [13••].

The lack of antiretroviral options limits the ability of healthcare workers in developing countries to intervene appropriately in the event of toxicity [14,15•] or treatment failure. There is growing concern that unacceptable toxicities related to mitochondrial toxicity may limit the usefulness of stavudine (D4T) [16,17•]. The WHO [18] recommends D4T use for first-line therapy in developing countries. It is widely used in national antiretroviral programmes because of its efficacy and low cost. Two studies in southern Africa [19,20••] however, found surprisingly higher rates of lactic acidosis than earlier reports from other settings. Interestingly, female sex and obesity were identified as risk factors for symptomatic hyperlactataemia. Useful alternatives to D4T such as tenofovir and abacavir are more expensive and often not available.

Efforts to improve accessibility and the utility of protease inhibitors in developing countries are yielding positive results. Lopinavir coformulated with ritonavir is the most common protease inhibitor used in developing countries and is an important component of second-line regimens. Previous formulations of lopinavir/ritonavir and ritonavir required cold storage facilities, placing a strain on patients and antiretroviral programmes in areas without electricity. A new heat stable tablet formulation of lopinavir/ritonavir with a reduced pill burden and food effect [21•] has replaced the soft-gel capsule. Encouraging pharmacokinetic and efficacy data [22–24] from new agents such as darunavir, etravirine, maraviroc and raltegravir have improved the outlook for treatment experienced patients in western countries. With the prospects of generic versions of newer and more expensive agents diminished, availability will be restricted to a small minority of patients receiving care at research sites or special projects.

Finally, a knowledge gap remains on the influence of behavioural and cultural practices on HIV therapy. Preclinical studies [25] suggest that the potential for unfavourable drug interactions exists between commonly used herbal agents and NNRTIs and protease inhibitors. Traditional medicine use is widespread [26] and embedded in culture. For the vast majority of agents, little is known of their nature, mechanism of action, efficacy or toxicity profiles.

Genetics

NNRTIs and protease inhibitors are metabolized by cytochrome P450 (CYP450) enzymes [27•]. Accumulating evidence suggests that differences in NNRTI metabolism are due to polymorphisms of genes encoding metabolizing enzymes. The frequency of these polymorphisms varies with race and their effects may be clinically significant. Earlier work by Haas and colleagues [28] demonstrated an association between central nervous system toxicity, higher efavirenz levels and CYP2B6 516 polymorphisms that occurred more commonly in blacks. Recent studies [4•,29] also report associations between NNRTI levels and racially distributed genetic differences. Analogous to earlier reports with efavirenz, CYP2B6 516 variant alleles were associated with higher nevirapine concentrations. A 1.5-fold increase (95% confidence interval, 1.18–1.84) in 12 h nevirapine concentrations was observed in TT versus GG individuals in one Ugandan study [30•]. Efforts to identify other pharmacogenetic factors which may affect the pharmokinetics of antiretrovirals are ongoing.

Adherence

Optimal adherence is necessary for successful antiretroviral therapy. Treatment interruptions, however, do occur and may be beyond the patient's control, for example due to illness or drug stock-outs. Interruptions may lead to the selection of resistant virus [31], particularly when antiretrovirals in treatment combinations have different half lives. This results in a state of 'functional monotherapy' with the agent with the longer half life. For planned interruptions, several approaches to stopping therapy have been suggested [32•]. In settings where FDCs are the only available antiretrovirals, the only option available is the simultaneous stop with its associated risks.

NNRTIs have a low genetic barrier to resistance, raising concerns that NNRTI-based regimens may be suboptimal in the absence of near perfect adherence. Earlier work [33] with nonboosted protease inhibitors revealed markedly higher rates of virologic failure when adherence rates dropped below 95%. A recent study [34•], however, observed a linear relationship between virologic outcomes and adherence, when adherence levels increased beyond 50%. This suggests that NNRTI-based regimens may have comparable efficacy to protease inhibitor-based regimens at intermediate levels (70–94%) of adherence. This finding is important because protease inhibitors may not be available in many resource-limited settings.

Food and nutrition

Antiretroviral absorption and metabolism may be affected by concurrent food intake and by malnutrition. In clinical practice, up to a third of patients in African

settings are malnourished and malnutrition is a risk factor for early mortality after commencement of antiretrovirals [35]. Lack of food makes it difficult to follow prescription advice for drugs which should be taken with meals. Since opportunistic infections are common and limit the ability of patients to generate income, food and nutrition supplements are often needed. Although nutritional supplements are not routinely provided in most antiretroviral clinics, recent evidence indicates quality of life in HIV-positive patients is improved with their use. In one blinded placebo-controlled trial [36•], supplementation with vitamins B, C and E demonstrated a protective effect on depression in HIV-positive pregnant women. The prevalence of depression in that study was high (42.4%). In settings with limited access to counselling or antidepressants, such interventions may have a significant role.

At a population level, food insecurity is also linked to HIV, threatening millions of people in developing countries and increasing the vulnerability of African women to high-risk sexual behaviour [37•]. It is important to provide antiretrovirals as well as the necessary support to ensure that HIV-positive patients not only survive but thrive [38•]. A holistic model of HIV care integrating clinical care with nutritional support and poverty alleviation schemes is needed.

Children

Adherence in children is dependent on the dedication of care givers (in many cases elderly grandparents or older siblings). Antiretroviral formulations, therefore, must be not only palatable but convenient to administer. Following a review of available paediatric antiretrovirals, the WHO issued a call for production of scored tablets of D4T and zidovudine-based FDCs [39]. One paediatric tablet formulation containing D4T, lamivudine plus nevirapine has been developed [40•].

There is an urgent need to define appropriate doses of antiretrovirals for younger children. Children metabolize antiretrovirals differently to adults [41] and the pharmokinetics of antiretrovirals is less predictable. Recent studies [42•,43] indicate that young children are at risk of low antiretroviral exposure. In one pharmokinetic study [44••], inadequate efavirenz exposure was observed in up to 40% of South African children. It is postulated that the wide variability observed in efavirenz pharmokinetics is due to underlying pharmacogenetic differences among participants.

The limited data on the impact of malnutrition on antiretroviral pharmokinetics are troubling. One paediatric pharmokinetic study [45] using divided adult FDC tablets reported an independent association between lower nevirapine concentrations and stunting and higher nevirapine concentrations with wasting. Additional studies are required to confirm these preliminary findings and to investigate the effect of malnutrition on the pharmokinetics of other antiretrovirals. Paediatric dosing is further complicated by parallel dosing strategies utilizing body surface area (BSA) or body weight. Dosing by BSA is more accurate but more difficult to implement. In order to simplify dosing guidance in busy clinics, the WHO [46] is developing weight band dosing charts based on BSA. This tool's usefulness is dependent on the availability of paediatric FDC formulations which better approximate optimal antiretroviral doses in children.

Pregnancy

Pregnant women may require antiretrovirals for their own treatment or for prevention of mother to child transmission (PMTCT). Nelfinavir [47] (a drug commonly used for PMTCT) was withdrawn on identification of a contaminant but is expected to be available once safety and regulatory approvals are obtained. Combination antiretroviral therapy is preferred to single dose nevirapine (SDN) for PMTCT. It is suggested that the long half life of nevirapine [48] following SDN administration favours selection of resistant virus which may compromise a subsequent NNRTI-based regimen [49].

Two studies [50,51] have reported reductions of lopinavir concentrations requiring increases in lopinavir/ritonavir doses in pregnancy. A third study [52•] in predominantly black African women found only mild reductions in lopinavir concentrations and dosage adjustments were not necessary. The investigators speculate that pharmacogenetic differences could have played a role in their findings. It is also important to note that these three studies were conducted using the outdated soft-gel capsule formulation of lopinavir/ritonavir.

Co-endemic diseases

There is considerable overlap in the geographical distribution of the 'big three' diseases [tuberculosis (TB), malaria and HIV]. Although these diseases are the main focus of public health activities, many other viral, bacterial, fungal and parasitic diseases (including neglected tropical diseases) contribute to the significant disease burden in developing countries. It is necessary to understand the effect of these diseases or their treatments on antiretrovirals.

Tuberculosis

TB is the most common opportunistic infection in the setting of HIV in developing countries. The

emergence of multidrug resistant and extensive drug resistant strains of *Mycobacterium tuberculosis* presents a global threat to public health and HIV-infected populations [53•]. The synergistic nature of TB and HIV means that cotreatment is often necessary. Drug interactions, toxicities and the immune reconstitution inflammatory syndrome are common problems encountered in cotreated patients.

Reliance on rifampicin-based FDCs for TB control makes cotreatment with antiretrovirals difficult. Rifampicin induction of CYP450 reduces levels of coadministered substrates. Consistent with earlier findings, recent studies demonstrate significant reductions in exposure of protease inhibitors, and to lesser degree NNRTIs, with rifampicin use [54–58]. Although efavirenz use with rifampicin is recommended, there is still no consensus on dose modification with rifampicin use [59,60]. In many developing countries, adults are treated with 600 mg of efavirenz and anti-TB FDCs. When efavirenz is unavailable patients are often treated with nevirapine. A recent Thai study [61] suggests initiation of nevirapine with a 200 mg lead-in dose may be unnecessary in rifampicin-treated adults. Additional interaction and safety data in other populations are required to guide dosing recommendations for cotreated patients.

Although rifabutin does not reduce antiretroviral exposure, it is currently too expensive for use in developing countries. In contrast to HIV, drug development for TB has been painstakingly slow. Newer TB agents, effective against resistant TB and having favourable interactions with antiretrovirals are required [62•].

Malaria

Interactions involving HIV and malaria are complex, ranging from drug interactions to direct disease interactions. Like NNRTIs and protease inhibitors, many antimalarials are metabolized by CYP450. Cotreatment with antiretrovirals and antimalarials is unavoidable as malaria episodes may be frequent and severe. As artemisinin combination therapy (ACT) use becomes more widespread, pharmokinetic and safety interaction data in patients receiving antiretrovirals are needed. One study [63•], designed to evaluate the interaction between efavirenz and one commonly used ACT (amodiaquine plus artesunate) in healthy volunteers, was prematurely discontinued following marked transaminase elevations in the first two patients undergoing the interaction phase of the study. Markedly elevated levels of amodiaquine were observed in both patients.

Capacity building

Capacity building initiatives to strengthen antiretroviral programmes, support health workers and local research capacity are crucial to the success of HIV control efforts. Shortages of manpower, diagnostic facilities and drug treatments remain significant barriers to health delivery. The Clinton Foundation (HIV/AIDS initiative, http://clintonafrica.org/what-we-do/how-we-make-change/chai/) and other organizations provide ongoing support and subsidized inputs to antiretroviral programmes in poor countries.

Health workers need up-to-date information on the evolving field of HIV/AIDS treatment. Treatment and medicines information services are uncommon. With improving telecommunication access in developing countries, a real opportunity exists to provide advice to improve healthcare delivery in rural and remote settings. One such centre, the AIDS Treatment Information Centre (Infectious Diseases Institute Uganda, http://www.idi.ac.ug/, queries@atic.idi.co.ug), provides free services by telephone, e-mail and publications to African healthcare workers.

Harmonization of research is critical to produce sufficient evidence to guide treatment policies. Networking opportunities for scientists in developing countries can help to coordinate and expand research in developing countries. One such meeting for clinical pharmacologists was organized by the European Developing Countries Clinical Trials Partnership (EDCTP) in Uganda in June 2007. In addition, collaborations between north–south research institutions, for example HIVNAT (Netherlands, Australia, and Thailand) Network, NACCAP (Netherlands–African partnership for capacity building and clinical interventions against poverty-related diseases), and south–south partnerships are useful in scaling up research capacity in developing countries.

Conclusion

Optimization of therapy is crucial to ensure that regimens are effective and durable in developing countries. This can only be achieved by conducting pharmacology research in target populations, taking into account their socio-economic needs and cultural preferences. It is unfortunate that issues relating to access to treatment remain for the vast majority of those with HIV. Concerted efforts, therefore, must be made to attain set targets in order to improve the lives of those suffering from HIV in poor countries.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 407–408).

1 United Nations. Millennium development goals report; 2007. http://www.un.org/millenniumgoals/pdf/mdg2007.pdf. [Accessed 7 February 2008]

2 Sow PS, Otieno LF, Bissagnene E, *et al.,* Cohort Programme to Evaluate Access to Antiretroviral Therapy and Education Project Team. Implementation of an antiretroviral access programme for HIV-1-infected individuals in resource-limited settings: clinical results from 4 African countries. J Acquir Immune Defic Syndr 2007; 44:262–267.

3 Best BM, Goicoechea M, Witt MD, *et al.* A randomized controlled trial of therapeutic drug monitoring in treatment-naïve and -experienced HIV-1-infected patients. J Acquir Immune Defic Syndr 2007; 46:433–442.

4 • Gatanaga H, Hayashida T, Tsuchiya K, *et al.* Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. Clin Infect Dis 2007; 45:1230–1237.
Study demonstrating successful genotype-based efavirenz dose reduction in a developed country.

5 Jaffar S, Mbidde E, Robb A, *et al.* Scale-up of antiretroviral therapy in sub-Saharan Africa: priorities for public health research. Trop Med Int Health 2007; 12:1009–1010.

6 Hoehe MR, Timmermann B, Lehrach H. Human inter-individual DNA sequence variation in candidate genes, drug targets, the importance of haplotypes and pharmacogenomics. Curr Pharm Biotechnol 2003; 4:351–378.

7 Sebat J, Lakshmi B, Troge J, *et al.* Large-scale copy number polymorphism in the human genome. Science 2004; 305:525–528.

8 Vermund SH, Powderly WG, Infectious Diseases Society of America; HIV Medicine Association of IDSA. Developing a human immunodeficiency virus/acquired immunodeficiency syndrome therapeutic research agenda for resource-limited countries: a consensus statement. Clin Infect Dis 2003; 37 (Suppl 1):S4–S12.

9 Hosseinipour MC, Corbett AH, Kanyama C, *et al.* Pharmacokinetic comparison of generic and trade formulations of lamivudine, stavudine and nevirapine in HIV-infected Malawian adults. AIDS 2007; 21:59–64.

10 Marier JF, Borges M, Plante G, *et al.* Bioequivalence of abacavir generic and innovator formulations under fasting and fed conditions. Int J Clin Pharmacol Ther 2006; 44:284–291.

11 Monif T, Tippabhotla SK, Garg M, Singla AK. Comparative bioavailability/bioequivalence of two different stavudine 40 mg capsule formulations: a randomized, 2-way, crossover study in healthy volunteers under fasting condition. Int J Clin Pharmacol Ther 2007; 45:469–474.

12 Chompootaweep S, Poonsrisawat J, Xumseang P. Evaluation of the bioequivalence of zidovudine 100 mg capsules in healthy Thai male volunteers. J Med Assoc Thai 2006; 89 (Suppl 3):S79–S85.

13 •• Orsi F, D'Almeida C, Hasenclever L, *et al.* TRIPS post2005 and access to new antiretroviral treatments in southern countries: issues and challenges. AIDS 2007; 21:1997–2003.
This paper discusses the challenges facing developing countries regarding local production of generic antiretroviral agents and access to new antiretroviral drugs following the adoption of the Trade-Related Aspects of Intellectual Property Rights Agreement.

14 Nuesch R, Srasuebkul P, Ananworanich J, *et al.* Monitoring the toxicity of antiretroviral therapy in resource limited settings: a prospective clinical trial cohort in Thailand. J Antimicrob Chemother 2006; 58:637–644.

15 • Murphy RA, Sunpath H, Kuritzkes DR, *et al.* Antiretroviral therapy-associated toxicities in the resource-poor world: the challenge of a limited formulary. J Infect Dis 2007; 196 (Suppl 3):S449–S456.
A review of antiretroviral-related toxicities in developing countries.

16 Songa PM, Castelnuovo B, Mugasha EB, *et al.* Symptomatic hyperlactatemia associated with nucleoside analogue reverse-transcriptase inhibitor use in HIV-infected patients: a report of 24 cases in a resource-limited setting (Uganda). Clin Infect Dis 2007; 45:514–517; Epub 2007 Jul 5.

17 • Lowe SH, Hassink EA, van Eck-Smit BL, *et al.* Stavudine but not didanosine as part of HAART contributes to peripheral lipoatrophy: a substudy from the Antiretroviral Regimen Evaluation Study (ARES). HIV Clin Trials 2007; 8:337–344.
Contribution of stavudine to lipoatrophy in HAART.

18 WHO. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: recommendations for a public health approach (2006 revision). Geneva: World Health Organisation; February 2006.

19 Geddes R, Knight S, Moosa Y, *et al.* A high incidence of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis in HIV-infected patients in a South African context. S Afr Med J 2006; 96:722–724.

20 •• Wester CW, Okezie OA, Thomas AM, *et al.* Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. J Acquir Immune Defic Syndr 2007; 46:318–322.
A randomized controlled trial that found female gender and obesity to be predictive of hyperlactatemia and lactic acidosis in Botswana.

21 • Klein CE, Chiu YL, Awni W, *et al.* The tablet formulation of lopinavir/ritonavir provides similar bioavailability to the soft-gelatin capsule formulation with less pharmacokinetic variability and diminished food effect. J Acquir Immune Defic Syndr 2007; 44:401–410.
Pharmacokinetics of a new tablet formulation of lopinavir/ritonavir developed by melt extrusion technology.

22 Boffito M, Winston A, Jackson A, *et al.* Pharmacokinetics and antiretroviral response to darunavir/ritonavir and etravirine combination in patients with high-level viral resistance. AIDS 2007; 21:1449–1455.

23 Lalezari J, Goodrich J, DeJesus E, *et al.* Efficacy and safety of maraviroc plus optimized background therapy in viremic ART-experienced patients infected with CCR5-tropic HIV-1: 24-week results of a phase 2b/3 study in the US and Canada. [Abstract 104 a LB]. In: Program and Abstracts of the 14th Conference on Retroviruses and Opportunistic Infections; 25–28 February 2007; Los Angeles, California. Abstract 104 b LB.

24 Markowitz M, Nguyen BY, Gotuzzo E, *et al.* Rapid and durable antiretroviral effect of the HIV-1 integrase inhibitor raltegravir as part of combination therapy in treatment-naive patients with HIV-1 infection: results of a 48-week controlled study. J Acquir Immune Defic Syndr 2007; 46:125–133.

25 Mills E, Cooper C, Seely D, Kanfer I. African herbal medicines in the treatment of HIV: hypoxis and sutherlandia: an overview of evidence and pharmacology. Nutr J 2005; 4:19.

26 World Health Organization. Traditional medicine: growing needs and potentials. WHO Policy Perspectives on Medicines, no. 2; May 2002. Geneva. http://whqlibdoc.who.int/hq/2002/WHO_EDM_2002.4.pdf. [Accessed 7 February 2008]

27 • Walubo A. The role of cytochrome P450 in antiretroviral drug interactions. Expert Opin Drug Metab Toxicol 2007; 3:583–598.
A review of CYP450-mediated antiretroviral drug interactions.

28 Haas DW, Ribaudo HJ, Kim RB, *et al.* Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. AIDS 2004; 18:2391–2400.

29 Saitoh A, Fletcher CV, Brundage R, *et al.* Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. J Acquir Immune Defic Syndr 2007; 45:280–285.

30 • Penzak SR, Kabuye G, Mugyenyi P, *et al.* Cytochrome P450 2B6 (CYP2B6) G516T influences nevirapine plasma concentrations in HIV-infected patients in Uganda. HIV Med 2007; 8:86–91.
Pharmacokinetic study which demonstrated a 1.5-fold increase in 12 h nevirapine concentrations in CYP2B6 516 TT versus GG individuals.

31 Oyugi JH, Byakika-Tusiime J, Ragland K, *et al.* Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. AIDS 2007; 21:965–971.

32 • Taylor S, Boffito M, Khoo S, *et al.* Stopping antiretroviral therapy. AIDS 2007; 21:1673–1682.
Expert opinion on various strategies for stopping antiretroviral therapy.

33 Paterson DL, Swindells S, Mohr J, *et al.* Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. Ann Intern Med 2000; 133:21–30; Erratum 2002; 136:253..

34 • Nachega JB, Hislop M, Dowdy DW, *et al.* Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. Ann Intern Med 2007; 146:564–573.
An observational adherence study utilizing pharmacy refill data.

35 Wandera B, Castelnuovo B, Kiragga A, *et al.* The impact of malnutrition on survival and immunological response in HIV infected patients starting antiretroviral therapy (ART) in Uganda. In: Program and Abstracts of the 4th IAS Conference on HIV pathogenesis, treatment and prevention; 22–25 July 2007; Sydney, Australia. Abstract MOPEB092.

36 • Smith Fawzi MC, Kaaya SF, Mbwambo J, *et al.* Multivitamin supplementation in HIV-positive pregnant women: impact on depression and quality of life in a resource-poor setting. HIV Med 2007; 8:203–212.
This study demonstrates evidence that vitamin B, C and E supplementation reduces risk of elevated depressive symptoms.

37 • Weiser SD, Leiter K, Bangsberg DR, *et al.* Food insufficiency is associated with high-risk sexual behavior among women in Botswana and Swaziland. PLoS Med 2007; 4:1589–1597; discussion 1598.
A cross-sectional population-based study in southern Africa.

38 • Russell S, Seeley J, Ezati E, *et al.* Coming back from the dead: living with HIV as a chronic condition in rural Africa. Health Policy Plan 2007; 22:344–347.
This report highlights the role of economic and social support in rebuilding lives and livelihoods of HIV patients.

39 World Health Organization. WHO expert working group meeting to determine preferred ARV medicines for treating and preventing HIV-infection in younger children; 23–25 October 2007. Geneva

40 L'homme RF, Dijkema T, Warris A, *et al.* Pharmacokinetics of two generic
• fixed-dose combinations for HIV-infected children (Pedimune Baby & Pedimune Junior) are similar to the branded products in healthy adults. J Antimicrob Chemother 2007; 59:92–96.
A pilot study demonstrating comparable pharmacokinetics of new paediatric antiretrovirals to branded drugs.

41 Jullien V, Urien S, Hirt D, *et al.* Population analysis of weight-, age-, and sex-related differences in the pharmacokinetics of lopinavir in children from birth to 18 years. Antimicrob Agents Chemother 2006; 50:3548–3555.

42 Verweel G, Burger DM, Sheehan NL, *et al.* Plasma concentrations of the HIV-
• protease inhibitor lopinavir are suboptimal in children aged 2 years and below. Antivir Ther 2007; 12:453–458.
Reports significantly more children less than 2 years had inadequate plasma concentrations with recommended dose of lopinavir/ritonavir.

43 Burger DM, Verweel G, Rakhmanina N, *et al.* Age-dependent pharmacokinetics of lamivudine in HIV-infected children. Clin Pharmacol Ther 2007; 81:517–520.

44 Ren Y, Nuttall JJ, Egbers C, *et al.* High prevalence of sub-therapeutic plasma
•• concentrations of efavirenz in children. J Acquir Immune Defic Syndr 2007; 45:133–136.
The first study to report efavirenz concentrations in African children. Subtherapeutic concentrations of efavirenz were observed in 40% of sampled children. Marked bimodality in efavirenz concentrations was also demonstrated.

45 Ellis JC, L'homme RF, Ewings FM, *et al.* Nevirapine concentrations in HIV-infected children treated with divided fixed-dose combination antiretroviral tablets in Malawi and Zambia. Antivir Ther 2007; 12:253–260.

46 World Health Organization. WHO generic tool for assessing paediatric ARV dosing. 2007. http://www.who.int/entity/hiv/paediatric/generictool/en/index.html. [Accessed 7 February 2008]

47 World Health Organization. WHO statement on Roche's Viracept recall; 8 June 2007.

48 Muro E, Droste JA, Hofstede HT, *et al.* Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose nevirapine: implications for intervention studies. J Acquir Immune Defic Syndr 2005; 39:419–421.

49 Flys TS, Mwatha A, Guay LA, *et al.* Detection of K103N in Ugandan women after repeated exposure to single dose nevirapine. AIDS 2007; 21:2077–2082.

50 Manavi K, McDonald A, Al-Sharqui A. Plasma lopinavir trough levels in a group of pregnant women on lopinavir, ritonavir, zidovudine, and lamivudine. AIDS 2007; 21:643–645.

51 Stek AM, Mirochnick M, Capparelli E, *et al.* Reduced lopinavir exposure during pregnancy. AIDS 2006; 20:19.31–19.39.

52 Lyons F, Lechelt M, De Ruiter A. Steady-state lopinavir levels in third trimester
• of pregnancy. AIDS 2007; 21:1053–1054.
This study found lopinavir levels in the third trimester closer to the nonpregnant state than earlier reports.

53 Andrews JR, Shah SN, Gandhi N, *et al.* Multidrug-resistant and extensively drug-
• resistant tuberculosis: implications for the HIV epidemic and antiretroviral therapy rollout in South Africa. J Infect Dis 2007; 196 (Suppl 3):S482–S490.
A review of drug-resistant TB in South Africa.

54 Ribera E, Azuaje C, Lopez RM, *et al.* Pharmacokinetic interaction between rifampicin and the once-daily combination of saquinavir and low-dose ritonavir in HIV-infected patients with tuberculosis. Antimicrob Chemother 2007; 59:690–697.

55 Matteelli A, Regazzi M, Villani P, *et al.* Multiple-dose pharmacokinetics of efavirenz with and without the use of rifampicin in HIV-positive patients. Curr HIV Res 2007; 5:349–353.

56 Rolla VC, da Silva Vieira MA, Pereira Pinto D, *et al.* Safety, efficacy and pharmacokinetics of ritonavir 400 mg/saquinavir 400 mg twice daily plus rifampicin combined therapy in HIV patients with tuberculosis. Clin Drug Investig 2006; 26:469–479.

57 Burger DM, Agarwala S, Child M, *et al.* Effect of rifampin on steady-state pharmacokinetics of atazanavir with ritonavir in healthy volunteers. Antimicrob Agents Chemother 2006; 50:3336–3342.

58 Cohen K, van Cutsem G, Boulle A, *et al.* Nonnucleoside reverse transcriptase inhibitors and rifampicin. In: Program and Abstracts of the 39th Annual Congress of the South African Pharmacological Society; 2005; Cape Town, South Africa. Abstract 22.

59 Brennan-Benson P, Lyus R, Harrison T, *et al.* Pharmacokinetic interactions between efavirenz and rifampicin in the treatment of HIV and tuberculosis: one size does not fit all. AIDS 2005; 19:1541–1546.

60 Manosuthi W, Kiertiburanakul S, Sungkanuparph S, *et al.* Efavirenz 600 mg/day versus 800 mg/day in HIV-infected patients with tuberculosis receiving rifampicin: 48 weeks results. AIDS 2006; 20:131–132.

61 Anchalee A, Manosuthi W, Kantipong P, *et al.* Pharmacokinetics and 12 weeks efficacy of nevirapine, 400 mg vs 600 mg per day in HIV-infected patients with active TB receiving rifampicin: a multicenter study. In: Program and Abstracts of the 14th Conference on Retroviruses and Opportunistic Infections; 25–28 February 2007; Los Angeles, California, USA. Abstract 576.

62 Pepper DJ, Meintjes GA, McIlleron H, Wilkinson RJ. Combined therapy for
• tuberculosis and HIV-1: the challenge for drug discovery. Drug Discov Today 2007; 12:980–989.
A review of current and novel agents for treatment of HIV and TB coinfection.

63 German P, Greenhouse B, Coates C, *et al.* Hepatotoxicity due to a drug
• interaction between amodiaquine plus artesunate and efavirenz. Clin Infect Dis 2007; 44:889–891.
Unexpected hepatotoxicity following cotreatment with antiretrovirals and antimalarials.