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How developing world concerns need to be part of drug development plans: a case study of four emerging antiretrovirals

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Clinical trials are usually designed to meet registration requirements in developed countries, and do not always address key concerns for use in developing countries. Four late-stage investigational new drugs – rilpivirine, etravirine, raltegravir and maraviroc – show potential to improve antiretroviral therapy. However, a number of issues could limit their use in developing countries, including dose selection, treatment strategy, combination with other drugs, use in specific populations and reliance on expensive tests. Key research questions relevant for developing countries need to be answered early in the drug development process to ensure maximum benefit for the majority.

Introduction

Although the majority of people infected with HIV/AIDS live in the developing world, there are often long delays between the registration of a new antiretroviral drug in the West and its inclusion in national healthcare systems in developing countries. For example, the World Health Organization (WHO) included tenofovir in first-line antiretroviral therapy for resource-limited settings in 2006 [1], five years after the FDA registered it. As of May 2008, only three African countries have included tenofovir in their guidelines for first-line regimens (Namibia, Lesotho and Zambia).

Why does it take so long to integrate new life-saving drugs in treatment guidelines of developing countries? Affordability and timely drug registration are recognized issues [2], but another limiting factor that is much more poorly recognized is the lack of relevant studies providing evidence for added value above existing treatment algorithms. We, and others, have argued that this is intrinsically linked to the lack of profitability in resource-limited settings [2,3]: HIV-infected populations differ between developed and developing countries, the latter including significant numbers of children, women of child-bearing age and people coinfected with tuberculosis, malaria and other infectious diseases. This paper focuses on four antiretroviral drugs that are advanced in development or that have been recently approved to provide an analysis of to what extent current research and development of HIV drugs appropriately addresses the needs of developing countries (Table 1).

Three drugs, maraviroc, raltegravir and etravirine, have been approved by the FDA since mid-2007, while the fourth drug under discussion here – rilpivirine – is currently the most advanced drug in the HIV pipeline. The information presented in this paper is on the basis of interviews conducted with scientific opinion leaders, and a review of the literature. We used PubMed and the clinical trials database of the US National Institutes of Health (http://www.clinicaltrials.gov/) to search the terms 'rilpivirine', 'tmc 278', 'maraviroc', 'raltegravir', 'etravirine' and 'tmc 125'. We also contacted the originator companies (Tibotec, Merck and Pfizer) for the four drugs under discussion with a series of questions. Tibotec and Merck requested the signing of confidentiality agreements before providing information beyond what is already in the public domain. We declined the signing of confidentiality agreements because we believe that it would have prevented starting an open dialog in the scientific community. Pfizer did not respond.

Clinical development of antiretrovirals

Antiretrovirals are primarily made for developed country markets and clinical trials are designed to meet the requirements for registration in these countries. Key research questions relevant for resource-limited settings are often only raised long after a drug has been registered and marketed in the USA and Europe. The gap in the currently available knowledge relating to how

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TABLE 1

Drug class, presentation and approval status of four emerging antitretrovirals

Drug name	Brand name	ARV class	Producer	Presentation	Approval status
Rilpivirine		NNRTI	Tibotec	Phase III trial will be 75 mg*	Phase IIb
Etravirine	Intelence	NNRTI	Tibotec	100 mg tablet	US FDA approved 18/01/2008
Maraviroc	Selzentry	CCR5 inhibitor	Pfizer	150 mg and 300 mg tablets	US FDA approved 06/08/2007
Raltegravir	Isentress	Integrase inhibitor	Merck	400 mg tablet	US FDA approved 12/11/2007

* Since this paper was submitted, Tibotec announced that because of toxicity concerns they will investigate a lower dose (25 mg) in Phase III trials.

antimalarial drugs and antiretrovirals interact [4] is a good example: the latest WHO guidelines [1] do not provide evidence-based guidance on how to use antimalarials together with antiretrovirals, despite the fact that 80% of HIV-infected individuals live in regions where malaria is endemic (http://www.who.int/malaria/malariandhivaids.html). This is in contrast to current practice in the developed world, where drug regulatory authorities often insist that data regarding a drug's use in particular populations be submitted. For example, the FDA [5] has included incentives and obligations to encourage the submission of data for pediatric use since 1997, an initiative that was finally adopted by the European Agency for the Evaluation of Medicinal Products (EMEA) in January 2007 [6].

The arrival of antiretrovirals with new mechanisms of action and, hence, greater potency against resistant strains points to a potential shift in how HIV/AIDS will be treated in the future [7–10]. The extent to which these innovations will benefit the majority of those affected by the disease who live in the developing world will depend on the availability of relevant clinical data: efficacy in minority populations, interaction with drugs to treat common coinfections and different formulations (combinations and dosages). Moreover, in high-burden countries public health authorities need cost-effectiveness data for optimal integration into existing treatment algorithms. Thus there are considerations both in terms of patient care (improved safety and efficacy) and public health (sustainability).

Rilpivirine is a second-generation non-nucleoside reverse-transcriptase inhibitor (NNRTI) showing *in vitro* antiretroviral activity up to 20 times greater than efavirenz or nevirapine, the two most common drugs used in first-line regimens in developing countries. Rilpivirine is effective against HIV-1 variants with key NNRTI mutations, and there is a high genetic barrier to the development of rilpivirine resistance. Data from a 48-week Phase II trial show noninferiority to efavirenz even at the lowest dose of 25 mg. From a safety perspective the compound was found to have less central nervous system side effects and a better lipid profile than efavirenz [8].

Etravirine is a non-nucleoside reverse-transcriptase inhibitor with potent activity against HIV strains resistant to current NNRTIs. It has been shown to be highly effective in treatment-experienced patients in combination with other active compounds [11].

Raltegravir is an integrase inhibitor, a new class of antiretrovirals showing *in vitro* activity against virus strains resistant to all existent antiretroviral drug classes. Licensing for treatment-experienced patients was granted in December 2007, and trials are currently underway for treatment-naive (Phase II) patients (http://www.fda.gov/oashi/aids/listserve/listserve2007.html).

Maraviroc belongs to the HIV entry inhibitors class, a new class of drugs that act to block viral entry into the cell. Different HIV clades use different coreceptors, either CCR5 or CXCR4, to bind to CD4 cells. Maraviroc interacts specifically with CCR5, and its efficacy strongly depends on the CCR5 tropism at treatment initiation [12].

The following points of importance to developing countries will be considered in this case study: dose selection, comparability and compatibility with other ARVs, and use in specific populations.

Dose selection

Active pharmaceutical ingredients constitute the main cost of drug manufacture [13]. In developed countries, where drugs are sold at a high profit, this cost only represents a fraction of the market price. In the developing world, where generic competition allows costs to approach manufacturing costs, the amount of active pharmaceutical ingredient is crucial. The 75-mg dose of rilpivirine has been selected for further development. Data presented at the CROI meeting in 2007 [8] showed no significant difference in efficacy between the 25, 75 and 150 mg doses. Virological (viral load reductions and the percentage of patients with viral load below 50 copies) and immunological (increase in CD4 count) responses were not significantly different. Particularly for treatment-naïve patients, formulating rilpivirine at a lower dose could reduce the cost and significantly enhance access in the developing world. In addition to cost concerns, there is evidence that, at least for some drugs (efavirenz, e.g. [14]), there is a correlation between plasma drug concentration and the risk of developing toxicity. Therefore, these lower doses should be tested in clinical studies (After this paper was submitted, Tibotec announced they would include a lower dose for rilpivirine in clinical trials.).

Treatment strategy

Tibotec is developing rilpivirine for the treatment of antiretroviral-naïve patients in combination with other antiretrovirals [15]. However, on the basis of its *in vitro* virological profile and specific pharmacokinetics it is reasonable to expect excellent safety and efficacy in treatment-experienced patients. Etravirine, a similar compound developed by the same company, has been shown to be highly effective in treatment-experienced patients, providing an additional rationale for this hypothesis [11].

A proof-of-principle study with rilpivirine in treatment-experienced patients was performed but results have not been made public. Etravirine unfortunately has less favorable drug product characteristics – high pill burden and a difficult manufacturing process using a specific spray dry technology – limiting its potential in the developing world [16]. Tibotec is the developer of both of these new NNRTI compounds. Could they have economic

reasons for choosing to reserve one compound for the treatment of ARV-naïve and the other for the treatment of ARV-experienced patients? On the basis of this development strategy, initial approval of rilpivirine by regulatory authorities in the developed world will probably limit the indication to the treatment of ARV-naïve patients. We believe this will make it harder for national regulatory authorities and guideline committees to approve it for use in treatment-experienced populations.

Etravirine (also known as Intelence or TMC125) was approved by the FDA on 18 January 2008 for use in combination with at least two other antiretroviral agents for the treatment of adults with HIV-1 infection. Apart from being complex to manufacture, the drug was recently granted a patent in India, which will greatly limit the ability of Indian generics manufacturers to produce this drug (http://www.kaisernetwork.org/daily_reports/rep_index.cfm?DR_ID=50350).

Combination with other antiretrovirals

The clinical development plan for rilpivirine includes studies in combination with tenofovir/emtricitabine, zidovudine/lamivudine or abacavir/lamivudine. These form the backbone of first-line regimens in the developed world, and Tibotec hopes to show added value over the existing NNRTIs.

In the developing world, however, there might be an interest in preserving the first generation of NNRTIs, such as efavirenz and nevirapine, which are widely used and have proven efficacy, and reserve this second-generation compound for a later stage in the treatment sequence. Only if baseline resistance in newly infected individuals against efavirenz and nevirapine rises above a certain threshold would it be justified to replace these drugs by newer NNRTIs earlier in the treatment sequence. Additionally, for patients who have been treated with NNRTIs and NRTIs (nucleotide reverse transcriptase inhibitors), the efficacy of rilpivirine may be lower unless it is combined with other fully active drugs such as boosted protease inhibitors [17,18].

Currently, boosted protease inhibitors are the standard, indeed the only, choice for second-line treatment. Clinical data for raltegravir show good efficacy in highly treatment-experienced patients [19]. Preliminary pharmacokinetic data have shown an increase in the plasma concentration of raltegravir in the presence of atazanavir. This is because atazanavir is a strong inhibitor of UDP glucuronosyltransferase (*UGT1A1*), which is a mediator of raltegravir metabolization [20]. Thus, this combination may allow for an unboosted second-line regimen for NNRTI-dosed patients.

Two characteristics of current first-line treatment regimens have facilitated the scale-up of antiretroviral therapy in the developing world: low cost and simplicity (three-in-one fixed-dose combinations). Second-line antiretroviral therapy should be as affordable and simple as first-line regimens.

Raltegravir interacts negligibly with the NNRTI efavirenz, providing support for the approach of using the similar NNRTI rilpivirine in combination with raltegravir. It will be equally important to perform additional formulation work that provides a slow-release formulation that could lead to the development of a fixed-dose combination that would only need to be taken once a day. The use, at this stage, of raltegravir and rilpivirine would delay recourse to any of the boosted protease inhibitors, which have a higher complexity of drug–drug interactions, a higher pill burden and higher cost, all of which pose major challenges for their widespread use in resource-limited settings.

Use in specific populations

Currently, the limited human pharmacokinetic data [16] that are available do not support the use of rilpivirine together with rifampicin (a core drug to treat tuberculosis) because bioavailability of rilpivirine is reduced by 80% [21]. This poses a major problem for its use in HIV/TB coinfected individuals that represent a significant proportion of the HIV population in resource-limited settings. According to WHO up to 50% of TB patients in African countries are HIV positive (http://www.who.int/tb/challenges/hiv/facts/en/index.html), and this figure is rising to over 90% in some settings. This is another example of the importance of taking developing world considerations into account when undertaking clinical studies. Specific research needs to be incorporated in the development plans of new compounds, for example, to address whether rilpivirine is compatible with rifampicin *in vivo*, and this issue is further discussed in our concluding remarks.

This subject is also illustrated by the use (or non-use) of the new CCR5 inhibitor Maraviroc in resource-limited settings. Maraviroc is only fully active against HIV clades using the CCR5 coreceptor, and it is recommended that a viral tropism assay (Trofile^{TM}) is used to determine which HIV clade is present before starting Maraviroc treatment. FDA approved Maraviroc for use in treatment-experienced patients infected only with CCR5-tropic HIV-1 in July 2007, and EMEA has adopted a positive opinion [22] with the recommendation to grant a marketing authorization with the same indication. However, the tropism test is not widely available (currently it is only performed in CA, USA), expensive (US$ 1960; Mongram Biosciences as of August 2007) and is less than 90% specific. Moreover, complex interactions with PIs and NNRTIs are observed and dose adjustments warranted [23].

In rural resource-limited settings where basic monitoring tests are not always available it would be unrealistic to introduce new drugs that require additional complex laboratory tests before they can be used, particularly if the test is expensive and only available in the USA. Although an important treatment addition for high resource settings, this is an innovation that probably will not benefit people in resource-limited settings any time soon. (The costs of the tropism test alone are 20 times the current annual spend on lab tests per patient in South Africa [24].)

Conclusions

Simplified first-line regimens have been a cornerstone to scale up ART in resource-limited settings. The priority today is to develop more robust first- and second-line regimens that are simple, affordable and compatible with patient and disease profiles in the developing world.

Antiretrovirals with a new mechanism of action are heralded in the developed world for their potential to change the treatment paradigm. If resource-poor settings are to benefit maximally from these innovations we need to ensure that robust data from clinical trials support their use in these environments. Necessary research includes lower dose efficacy studies with rilpivirine, interaction studies between raltegravir and rilpivirine, formulation work for a once daily dosing schedule of raltegravir, and concentration and effect (pharmacokinetic–pharmacodynamic) data for this regi-

men. Studies should also compare the efficacy of rilpivirine and/or raltegravir-containing regimens against current WHO recommendations for second-line therapy.

Our analysis was limited by lack of free access to company information. Until such information is made more freely available, the rationale of companies' clinical development decisions will remain unclear and the scientific community will be unable to advise and contribute with research in resource-poor settings. In addition to the four drugs analyzed here, all other antiretroviral drugs currently in development should be reviewed for their potential use in resource-limited settings so that relevant trials can be included early on in clinical development. This will be possible only if the scientific community has better access to information and if companies feel accountable for the extent to which their clinical development plans will address high- and low-resource settings.

Pharmaceutical companies, in this case Merck (raltegravir) and Johnson & Johnson/Tibotec (rilpivirine), have a responsibility to initiate and contribute to studies that are relevant for resource-limited settings if they are seriously committed to contribute to global health. However, this is not their job alone. The scientific community should also play a bigger part than is the case today in carrying out such studies that are of global public benefit. Public funding could be sought for such research as long as there is very clear agreement between the private and the public sector on future accessibility in terms of price, in-country registration and possible licensing to other producers [25].

Regulatory agencies also have an important part to play by requiring data for relevant populations in different settings as part of the drug approval process. Proactive steps should be taken by the originator companies that hold the intellectual property and clinical data for the compounds.

The issues outlined for these emerging antiretrovirals are a symptom of the general concern that the drug research and development agenda rarely includes the specific concerns of the developing world, where 90% of people with HIV/AIDS reside [26].

Greater consideration should be given by all stakeholders to ensure that promising new drugs are made as affordable as possible, as soon as possible. To date, the history of antiretroviral drug development has shown that these two basic needs of the developing world are usually only considered long after a new medicine has been available in the West, if they are considered at all.

Although, for some diseases, the creation of product development partnerships is helping to address enormous innovation gaps [27], the situation for HIV drug development is different because HIV drug development for the Western market remains profitable.

Considerable international funding is available to support HIV/AIDS care in the developing world and this has created a viable low-cost, high-volume market for products aimed at developing countries. Pharmaceutical companies should make the development and delivery of effective and affordable medicines for high- and low-resource settings an integral part of their business model.

Conflict of interest

Jens van Roey has been employed by Tibotec but was not involved in the development of the drugs mentioned in this article.

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References

1 World Health Organization (2006) Antiretroviral Therapy for HIV Infection in Adults and Adolescents: Recommendations for a Public Health Approach. WHO
2 Ford, N. *et al.* (2007) Treating HIV in the developing world: getting ahead of the drug development curve. *Drug Discov. Today* 12, 1–3
3 Nathan, C. (2007) Aligning pharmaceutical innovation with medical need. *Nat. Med.* 13, 304–308
4 Khoo, S. *et al.* (2005) The potential for interactions between antimalarial and antiretroviral drugs. *AIDS* 19, 995–1005
5 FDA Modernization Act of 1997 (http://www.fda.gov/cder/guidance/105-115.html)
6 Regulation (EC) No. 1901/2006 of the European Parliament and of the council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No. 726/2004 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol1/reg_2006_1901/reg_2006_1901_en.pdf)
7 Treatment Action Group (2007) The 2007 pipeline report. In *Experimental Treatments and Preventive Therapies for HIV, Hepatitis C, and Tuberculosis*. TAG (http://www.aidsinfonyc.org/tag/tx/pipeline0707.pdf)
8 Pozniak, A. (2007) 48-week primary analysis of trial TMC278-C204: TMC278 demonstrates potent and sustained efficacy in ART-naïve patients. *14th Conference on Retroviruses and Opportunistic Infections*, Los Angeles, 25–28 February (Abstract #144LB)
9 Esté, J. and Telenti, A. (2007) HIV entry inhibitors. *Lancet* 370, 81–88
10 Dayam, R. (2007) HIV-1 integrase inhibitors, an emerging clinical reality. *Drugs in R&D* 8, 155–168
11 Cahn, P. *et al.* (2007) Pooled 24-week results of DUET-1 and -2: TMC125 vs placebo in 1203 treatment-experienced HIV-1-infected patients. *Program and Abstracts of the 47th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC)*, Chicago, Illinois, 17–20 September (Abstract H-717)
12 Saag, M. *et al.* (2007) A multicenter, randomized, double-blind, comparative trial of a novel CCR5 antagonist, maraviroc versus efavirenz, both in combination with Combivir (zidovudine [ZDV]/lamivudine [3TC]), for the treatment of antiretroviral naive patients infected with R5 HIV 1: week 48 results of the MERIT study. *4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention*, Sydney, Australia, 22–25 July, 2007 (Abstract WESS104)
13 Yeni, P. *et al.* (2007) TMC278, a next-generation NNRTI, demonstrates potent and sustained efficacy in ARV-naive patients: week 48 primary analysis of study TMC278-C204. *11th European AIDS Conference*, Madrid (Abstract P7.2/08)
14 *Antiviral Solid Dispersions*. European Patent Office. International Publication Number: WO 2001/022938 (05.04.2001, Gazette 2001/14)
15 Pinheiro, E. *et al.* (2006) Examining the production costs of antiretroviral drugs. *AIDS* 20, 1745–1752
16 Marzolini, C. *et al.* (2001) Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 5, 71–75
17 Woodfall, B. *et al.* (2006) Impact of NNRTI and NRTI resistance on the response to the regimen of TMC125 Plus 2 NRTIs in study TMC125-227. *Eighth International Congress on Drug Therapy in HV Infection*, Glasgow, 12–16 November (Abstract PL5.6)
18 Cohen, C. *et al.* (2006) Efficacy and safety results at 48 weeks with the novel NNRTI, TMC125, and impact of baseline resistance on the virologic response in study TMC125-C223. *16th International AIDS Conference*, Toronto, Canada, 13–18 August (Abstract No. TuPE0061)
19 Cahn, P. (2007) Raltegravir: a new antiretroviral class for salvage therapy. *Lancet* 369, 1261–1269
20 Product Information: ISENTRESS oral tablets, raltegravir oral tablets. Merck & Co., Inc., Whitehouse Station, NJ, 2007
21 van Heeswijk, R. *et al.* (2006) The effects of CYP3A4 modulation on the pharmacokinetics of TMC278, an investigational non-nucleoside reverse

transcriptase inhibitor. *Poster 47, 7th International Workshop of Clinical Pharmacology*, April 2006 (Abstract 74)
22 European Medicines Agency. Committee for medicinal products for human use. *Summary of Positive Opinion for Celsentri*. EMEA/CHMP/255299/2007 (http://www.emea.europa.eu/pdfs/human/opinion/Celsentri_25529907en.pdf)
23 Tseng, A. (2007) *Drug Interactions with CCR5 Antagonists*. Toronto General Hospital (http://www.tthhivclinic.com/pdf/CCR5-int.pdf)
24 Cleary, S. *et al.* (2006) The cost-effectiveness of antiretroviral treatment in Khayelitsha, South Africa – a primary data analysis. *Cost Effect. Resour. Allocat.* 4, 4–20
25 Chokshi, D.A. and Rajkumar, R. (2007) Leveraging university research to advance global health. *JAMA* 298, 1934–1936
26 Ford, N. and Torreele, E. (2001) Neglected diseases of global importance. *JAMA* 286, 23
27 Moran, M. *et al.* (2007) Partnership dynamics, issues and challenges. In: Global Forum Update on Research for Health Vol. 4 Global Forum for Health Research