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**Meeting Summary: Centre on Global Health Security**

# Innovation in Antiretrovirals to Meet Developing Country Needs

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## ACRONYMS

3TC	Lamivudine
ABC	Abacavir
ART	Antiretroviral treatment
ARV	Antiretroviral
ATV	Atazanavir
AZT	Zidovudine
CHAI	Clinton Health Access Initiative
DNDi	Drugs for Neglected Diseases initiative
EDCTP	European and Developing Countries Clinical Trials Partnership
EFV	Efavirenz
FDC	Fixed-dose combination
IP	Intellectual property
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
LPV	Lopinavir
RTV, r	Ritonavir
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
UN	United Nations
WHO	World Health Organization

## Background

On July 11, 2011, Chatham House, the Medicines Patent Pool, UNITAID and the World Health Organization (WHO), convened an expert meeting to identify the key innovation needs in the field of antiretroviral treatment for resource-limited settings, and to discuss the role of different actors in ensuring that the necessary innovation is undertaken.

The event took place a few weeks after the international community set new targets at the UN High-Level Meeting on HIV/AIDS, in particular to have 15 million people on treatment by 2015. Discussions at the meeting focused on what medicines will be required to achieve such targets, how to ensure they are developed and how to better integrate the needs of resource-limited settings in the short-, medium- and long-term HIV research agenda.

The work of the Medicines Patent Pool in negotiating licences to key intellectual property provided the backdrop for the meeting, given the opportunities it will generate for the development of medicines adapted to specific developing country needs, such as paediatric ARVs and fixed-dose combinations (FDCs).

The meeting was attended by selected experts representing a wide range of stakeholders involved in HIV-related innovation and treatment, including governments, international organizations, the pharmaceutical industry, public research organizations, foundations, civil society organizations, communities of people living with HIV and clinical experts.

## Implementing a Short-Term Innovation Agenda for Adult ARV Treatment

The first session focussed on identifying key innovation needs for resource-limited settings and opportunities to improve treatment regimens in the short term. Prof. Francois Venter, from South Africa, highlighted some of the challenges in antiretroviral treatment in developing countries, with a focus on South Africa [[presentation](#)]. Craig McClure of WHO outlined the main pillars of its Treatment 2.0 initiative for meeting current and future HIV treatment needs, and presented for the first time its priorities for short-term treatment optimisation [[presentation](#)]. Respondents were representatives from the government of Malawi, Johnson & Johnson, Cipla, the Government Pharmaceutical Organization of Thailand and the Clinton Health Access Initiative (CHAI).

Summary of discussions and key conclusions:

- There is a need for greater simplification and consolidation of treatment regimens, as advocated by the Treatment 2.0 initiative recently launched by WHO and UNAIDS<sup>1</sup>.
- Consolidation of treatment regimens should be balanced with the need to develop formulations that address specific needs in resource-limited settings and the optimization of existing treatment regimens.
- Key needs in resource-limited settings include medicines that are: better tolerated, low pill burden (ideally one pill, once day), more affordable, more “forgiving” of missed doses, requiring limited laboratory monitoring, appropriate for use by special populations (e.g. people with co-infections, pregnant women and children) and formulated as FDCs.
- Many formulations that meet WHO recommendations and could be of importance in developing countries have never been developed<sup>2</sup>.
- Opportunities for optimising current treatment regimens to address some of the above needs include dose reduction, improvements in process chemistry, re-formulation and co-formulation. Some of these may be achievable in the short term but others may require additional studies, including extensive clinical trials.
- Such approaches should be applied to the priority medicines for optimising treatment in the short term that have been identified by WHO<sup>3</sup>. These are:
  - For first-line therapy: TDF/3TC/EFV as a fixed dose combination
  - For second-line therapy: Atazanavir and low dose ritonavir (ATV/r) as a heat-stable FDC or a co-blister pack, combined with a NRTI backbone
- Current initiatives responding to priorities, based on statements at the Meeting, are:
  - FDC comprising TDF/3TC/EFV already on the market but there is a limited number of suppliers
  - Dose reduction studies for AZT and EFV ongoing
  - ATV/r FDC is under development by at least one producer

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<sup>1</sup> See WHO/UNAIDS, The Treatment 2.0 Framework For Action: Catalysing The Next Phase Of Treatment, Care And Support” available at <http://www.who.int/hiv/pub/arv/treatment/en/index.html>

<sup>2</sup> See document prepared by the Medicines Patent Pool, UNITAID and WHO with the list of missing drug formulations for HIV treatment submitted to the WHO Expert Committee on the Selection and Use of Essential Medicines, available at: [http://www.who.int/entity/selection\\_medicines/committees/expert/18/policy/Missing\\_HIV\\_formulations.pdf](http://www.who.int/entity/selection_medicines/committees/expert/18/policy/Missing_HIV_formulations.pdf). The documents was distributed as a background document for the Meeting

<sup>3</sup> Full analysis of WHO’s short-term priorities for antiretroviral optimization is available at: [http://whqlibdoc.who.int/publications/2011/9789241501941\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501941_eng.pdf)

- There are concerns among generic players over low profit margins in the industry and limited incentives to invest in new developments. The public sector may increasingly need to play a role.
- Development of new formulations needs to be accompanied by rapid approval, recommendation and uptake. There is a role for governments, international organizations and donors to support this.
- Cost of drugs remains a key concern and many countries face problems in meeting current treatment recommendations and switching to products with fewer side effects.
- Intellectual property barriers to the development of needed formulations exist in many cases. The Medicines Patent Pool is a mechanism that should help to overcome them through equitable, transparent and public-health oriented licenses.

### Responding to the Specific Needs of Paediatric HIV Treatment

With an estimated 2.5 million children living with HIV globally, the vast majority in Sub-Saharan Africa, and only 28% on antiretroviral treatment, paediatric HIV continues to be a major problem in developing countries. However, its virtual elimination in high-income countries has resulted in limited incentives for the development of paediatric HIV formulations.

Discussions at the meeting focussed initially on identifying current constraints and needs that should be addressed in the development of paediatric HIV medicines and subsequently on short- and medium-term priorities. Dr Ashraf Coovadia from the University of Witwatersrand (Johannesburg, South Africa) outlined the key needs on the ground based on a survey of caregivers, paediatricians, pharmacists and other health workers [[presentation](#)]. Marco Vitoria of WHO presented its recommendations for short-term priorities for paediatric HIV optimisation and the Drugs for Neglected Diseases initiative (DNDi) outlined its target product profile for paediatric HIV and the results of its own short- and medium-term prioritisation focussed on children under the age of 3 [[presentation](#)]. Respondents were representatives from UNICEF, the government of Botswana, Gilead Sciences and Matrix Laboratories.

Summary of discussions and key conclusions:

- Despite recent efforts to develop better paediatric formulations, and the introduction of regulatory incentives in certain jurisdictions, paediatric HIV remains a neglected area in drug development and many key priorities are not adequately addressed.
- Some of the main innovation needs in paediatric HIV are in the development of: more palatable formulations; solid FDCs suitable for children and infants; medicines that would enable less frequent administration; and medicines that can be taken with TB

treatment. Tablet size is also important for certain weight bands and heat-stability of products is key in some settings.

- Given the relatively limited (and decreasing) size of the market and its fragmentation, greater harmonisation of adult and paediatric guidelines is recommended; this would require the development of better paediatric formulations for certain key products (e.g. TDF, EFV, ATV/r), particularly for young children.
- Short-term development priorities for paediatric HIV, as outlined by WHO<sup>4</sup>, are:
  - LPV/r reformulation (40mg for LPV and 10mg for RTV).
  - AZT/3TC dispersible formulations.
  - Paediatric heat-stable ritonavir solid formulations (25mg).
  - Scored (twice on one side, once on the other) adult-strength dispersible fixed dose formulations of TDF/FTC/EFV.
- Current initiatives responding to priorities, based on statements at the Meeting, are:
  - Decision by the DNDi to enter the field of paediatric HIV drug development. DNDi priority is to develop a protease inhibitor-based 1<sup>st</sup> line for children under 3 years old suitable for dispersible tablet dosage.
  - ViiV Healthcare collaboration with CHAI and a generic producer to develop AZT/3TC dispersible formulations.
  - Abbott Laboratories: heat-stable ritonavir powder formulation currently under development.
  - Cipla: LPV/r sprinkles formulation for children under development.
  - Gilead Sciences: new TDF formulations suitable for children from 2 to 6 years old and from 6 to 12 submitted for regulatory approval.
- Some gaps remain, including data on the suitability of TDF for under 2-years old, adequate dosage proportion of RTV when combined with ATV in young children and a scored tablet FDC comprising TDF/3TC/EFV (important for greater alignment with adult treatment).
- New mechanisms to incentivise paediatric HIV development should be further explored (including, for example, prizes).

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<sup>4</sup> Full analysis of WHO's short-term priorities for paediatric antiretroviral drug optimization is available at: [http://whqlibdoc.who.int/publications/2011/9789241501941\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501941_eng.pdf)

- The Medicines Patent Pool could play a central role in making intellectual property (IP) available for the development of paediatrics by generic manufacturers and other institutions.

## Exploring Medium- and Long-term Opportunities for Innovation in ART

During the session on medium and long-term opportunities for innovation, the current research pipeline was discussed as well as areas that may require more research in the future. This included analysis of antiretrovirals under development, research on vaccines and on possible cure or “functional cure”. Current funding priorities of the key entities funding clinical trials in HIV were also discussed as well as research needs that have not been sufficiently addressed in the past.

Presentations were made by Dr. Emily Erbelding, NIH/NIAID Division of Acquired Immunodeficiency Syndrome (USA) [[presentation](#)] and Prof. Beatriz Grinsztejn from the Oswaldo Cruz Foundation (Fiocruz – Ministry of Health, Brazil) [[presentation](#)]. Respondents were representatives from Viiv Healthcare and Médecins sans Frontières.

Summary of discussion and key conclusions:

- There are a number of promising developments in the field of HIV research. These include:
  - Rich ARV pipeline with several products in late-stage clinical trials, including a number of FDCs.
  - Products with a potential for long-acting formulations that could represent important game-changers in antiretroviral treatment, under development<sup>5</sup>.
  - Promising developments in the field of vaccines and cure, although much research still required.
  - Greater involvement of researchers in developing countries through research partnerships and large research networks.
- Nevertheless, many areas have not been sufficiently addressed. Research should consider more the specificities of populations in resource-limited settings, such as genetic patterns, body mass index, nutritional status, previous medical history, HIV sub-types and other prevalent co-infections such as TB, HBV, HCV and malaria. It should also take more into account constraints in health systems infrastructure.

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<sup>5</sup> Specific products mentioned with a potential for long-acting formulation were: GSK-744, rilpivirine, elvucitabine, CMX-157 and GS 7340, some of which are already under study in such formulation

- Further research on adequate ARV dosage and regimens for TB co-infected patients is urgently needed as well as research on more effective treatment for other major opportunistic infections.
- Further research is also required on medicines used for third-line treatment, given very limited experience with such drugs in resource-limited settings.
- Calls were made for closer collaboration between originator and generic pharmaceutical companies early in the drug development process to reduce delays in getting new products to market in developing countries.
- The role of possible new treatment strategies (e.g. induction phase followed by maintenance with long-acting formulations) should be further explored.

### **Funding and Novel Incentives to Promote Innovation in HIV**

The Session on Funding and Novel Incentives to Promote Innovation in HIV looked at various current and proposed mechanisms to promote and support the development of HIV medicines that meet specific needs in resource limited settings. The Session was opened by Hon Stephen O' Brien, Parliamentary Under-Secretary of State for International Development of the United Kingdom. In his remarks, Hon. O'Brien recalled the targets adopted by the UN General Assembly in June and stressed that those targets could only be met if there was access to medicines that are inexpensive and better suited for use in resource-limited settings. He highlighted the important role the Medicines Patent Pool could play in sharing the benefits of innovation and stressed the UK government's support for the initiative.

The session included interventions from representatives from the Global Fund [[presentation](#)], UNITAID, Oxfam, the Technology Innovation Agency of South Africa [[presentation](#)], the European and Developing Countries Clinical Trials Partnership (EDCTP) [[presentation](#)], Knowledge Ecology International [[presentation](#)] and Ranbaxy, followed by discussions among all participants.

Summary of discussions and key conclusions:

- Different mechanisms may be used to support and incentivise the development of needed medicines and formulations, including advanced market commitments, subsidies, prize funds, mechanisms that signal markets, facilitate uptake or provide greater price transparency.
- Bilateral and multilateral donor institutions, as well as governments in developed and developing countries should evaluate options for proactively supporting the development of needed formulations.



- Low profit margins in the industry are a concern for the generic producers and limit incentives to invest in developing new formulations. Other players, such as public research organizations, have to play a role.
- Mechanisms to promote or reward innovation in this area should adequately integrate access considerations.
- Interventions that help to create, catalyse and shape markets have been important, such as those supported by UNITAID for paediatric and second-line treatment. The Global Fund's recent decision to engage in a new market shaping strategy could also yield important results.
- The possibility of introducing prize funds for specific targeted developments (e.g. in the paediatric field) should be further examined<sup>6</sup>, eg by UNITAID.
- WHO recommendations on priorities for drug optimisation in the short-term are very important as a basis to coordinate research efforts and ensure most urgent needs are met. Similar priority setting for the medium and long term should be undertaken.
- Funding priorities of donor institutions for clinical trials in resource-limited settings should, as far as possible, be aligned with agreed innovation priorities.
- The product development partnership model, widely used in other health fields, may be useful in HIV, particularly in areas often neglected by current research. DNDi's entry into the HIV paediatric field is very important in this respect.
- Specific concerns were raised in relation to middle-income countries, where prices of new, patented products are often prohibitive and voluntary licenses are often unavailable.
- The Medicines Patent Pool represents an opportunity to ensure newly developed products can be accessed more rapidly in developing countries at an affordable price, but it needs to be implemented alongside other mechanisms to enhance access to HIV medicines in developing countries.

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<sup>6</sup> A proposal for a prize fund that is currently under review by the WHO Consultative Expert Working Group (CEWG) on R&D was discussed. Other proposals being discussed by the CEWG, including a proposed R&D treaty were also mentioned.

## Conclusion

Meeting the new United Nations goal of treating 15 million people living with HIV by 2015 and continuing scale-up thereafter will require innovation in antiretroviral treatment and the participation of several stakeholder groups in developing the necessary medicines and ensuring they reach the people who need them. The meeting provided a good opportunity for a wide range of stakeholders to discuss innovation in HIV in the short, medium and long term and to review the priorities established by WHO and others for improving treatment. Simplification and optimisation of current treatment regimens were seen as key priorities in the short term. In the longer term, resource-limited settings need to be better integrated in the drug development process and new incentives may be required to ensure needed medicines and formulations are developed, and reach those in need. While key challenges remain, better coordinating research efforts to ensure that they are aligned with priorities in resource-limited settings will be central. Initiatives like the Medicines Patent Pool can be central to ensuring that the necessary intellectual property is available to adapt medicines to developing country needs and that new antiretroviral medicines developed reach those in need so that the benefits of innovation can be shared widely.

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