Action Plan for Scaling Up Early Diagnosis and Treatment of Children and Adolescents
Pontifical Academy of Sciences, Vatican City
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Introduction

On 17 November 2017, leaders of major pharmaceutical and medical technology companies, multilateral organizations, donors, governments, organizations providing or supporting services for children living with HIV, and other key stakeholders participated in a High-Level Dialogue on Scaling Up Early Diagnosis and Treatment of Children and Adolescents. The meeting was convened by His Eminence Peter Kodwo Appiah Cardinal Turkson, Prefect of the Dicastery for the Promotion of Integral Human Development, with PEPFAR, UNAIDS and Caritas Internationalis, and in close collaboration with the World Council of Churches-Ecumenical Advocacy Alliance, WHO, and EGPAF.[1]

Participants gathered to discuss how to reduce morbidity and mortality among children living with HIV, particularly by accelerating the development and introduction of priority paediatric formulations of antiretroviral drugs (ARVs). In contrast to the regular development of better ARVs for adults living with HIV over the past 20 years, there have been very few new optimal medicines made available for children. Existing ARVs are often bitter tasting, difficult to administer, inappropriate for low-resource settings, and with toxic side effects for growing bodies. The lack of suitable ARVs for children has contributed in part to low levels of treatment initiation, retention in care, and viral load suppression. Better paediatric formulations could save countless lives. More focused, accelerated, and coordinated action is therefore of the highest urgency.

With this in mind, concerned stakeholders have gathered on several occasions in 2016 and 2017 to exchange views on the policies and practices they believe should be changed to facilitate and expedite the research, development, approval, introduction and uptake of optimal drugs and formulations for infants, children and adolescents. Proposals have included both steps to make priority drugs in the pipeline quickly available in the short term as well as innovative mechanisms that could be put in place to facilitate and accelerate the development of paediatric formulations of drugs for HIV and other life-threatening diseases over the longer term. The High-Level Dialogue provided an opportunity for stakeholders to build on these conversations by putting forward a set of concrete actions they could take to better support the research, development, and introduction spectrum. These commitments, which also build on work within the Global Accelerator for Paediatric Formulations (GAP-f)[2] and the Start Free, Stay Free, AIDS Free Framework, form the basis of the Action Plan below.

Action Plan

In recognition of the urgency of making more optimal paediatric ARV formulations available in 2018 and beyond, the participants of the High-Level Dialogue[3] agreed to the following good faith commitments to focus, accelerate, and collaborate on the development, registration, introduction, and roll-out of the most optimal paediatric formulations and diagnostics[4]:

FOCUS on priority paediatric drugs and formulations

WHO committed to:

Action 1: Continue to host the Paediatric ARV Drug Optimization (PADO) process and update the list of priority products with a view to providing a consistent, clear, and harmonized set of products that will be communicated to industry and regulators in a timely manner, and ensure inclusion of PADO priority products in the WHO Expression of Interest list as soon as dosing is provided.

[1] WHO and EGPAF are co-conveners of the AIDS Free Working Group of the Start Free, Stay Free, AIDS Free framework.
[2] The Global Accelerator for Paediatric Formulations is a global partnership created to promote faster development, regulatory approval, and uptake of priority, optimal pediatric drugs and formulations to treat HIV.
[3] See Annex 1 for List of Participants.
[4] For additional, individual commitments made at the Consultation see Annex 2.

Action 2: Update treatment guidelines in a timely manner to ensure that more effective drugs are recommended for children as soon as pharmacokinetic (PK) and safety data is available.
Action 3: Continue to use the Paediatric ARV Working Group (PAWG) mechanism to provide recommendations on optimal dosing and ratios for formulation development.
Action 4: In collaboration with other partners, continue to revise the Optimal ARV Formulary and ensure its inclusion in Essential Medicine List.

Research networks committed to:

Action 5: Focus research efforts on optimal drugs and formulations as defined by PADO.

Pharmaceutical companies committed to:

Action 6: Prioritize PADO products in research and development plans.

SRAs committed to:

Action 7: Prioritize the review of Pediatric Study Plans (PSPs) and Paediatric Investigation Plans (PIPs) for paediatric ARVs on the list of PADO priority products over lower priority drugs.

Donors committed to:

Action 8: Support and fund clinical and implementation research to inform development and approval as well as use of paediatric formulations included in the PADO list.

Action 9: Only fund the procurement of drugs and formulations recommended by WHO that are included in the Optimal Formulary[5].

Implementing Partners committed to:

Action 10: Promote the revision of national procurement plans to align with WHO recommended regimens and the Optimal Formulary, and support the provision of reliable forecasts and the consolidation of orders.

ACCELERATE the development, review, and introduction of paediatric formulations

WHO committed to:

Action 11: Continue to convene the PAWG to provide advice to innovators prior to submission of PSPs/PIPs, communicate technical opinions to SRAs in a timely manner, and provide dosing and ratio recommendations to generics for development of new FDCs.
Action 12: Reestablish the Paediatric Regulatory network to accelerate national registration and facilitate in-country registration of specific products under the Collaborative procedure established by WHO.

Pharmaceutical companies committed to:

Action 13: In pre-clinical and clinical development, initiate paediatric formulation development as soon as a given drug shows potential public health impact in adults, soon after Phase II trials are completed.
Action 14: Include adolescents when conducting initial adult efficacy trials, where possible and practical, or conduct parallel trials with the goal of providing information to support licencing for adolescents at the same time as adults.
Action 15: In the design of paediatric PK and safety studies, use weight-based dosing and enroll all children above 4 weeks concurrently, unless a strong rationale exists for not doing so.
Action 16: Assess acceptability and palatability of formulations for low-resource settings at early stages of the formulations development.
Action 17: Engage in early and regular consultations with the PAWG on PIP/PSPs, as well as recommended dosing and ratios for FDC development.

[5] http://www.who.int/hiv/pub/paediatric/iatt-paediatric-hiv-2016/en/

Action 18: Take all possible measures to rapidly complete development of priority paediatric drugs and formulations in the pipeline, with the goal of providing the maximum number of new formulations by end of 2018, especially for infants and young children.

Research networks committed to:

Action 19: Undertake studies that use weight-based dosing, enroll all paediatric weight-band groups concurrently irrespective of age, and maximize opportunities to accelerate enrollment of subjects.

SRAs committed to:

Action 20: Accept and encourage the accelerated steps outlined in Actions 14-18 when evaluating paediatric development plans and reviewing drug applications and encourage formulation development to begin soon after Phase II dosing selection.

Donors committed to:

Action 21: Provide funding to support actions required for quickly introducing and scale-up new, optimal paediatric formulations.

Implementing Partners, and Faith-Based Organizations committed to:

Action 22: Support the early adoption of priority formulations and diagnostics and take steps to facilitate their wider roll-out, including by developing introductory guidance, materials, and other tools for health facilities.

The Global Accelerator Partners committed to:

Action 23: Call on regulatory authorities to expedite and simplify the review of priority paediatric formulations and diagnostics, including by:

- Making better use of sub-regional collaborative regulatory approval processes and the WHO Collaborative procedure for accelerated registration;
- Increasing reliance on evaluations and opinions of stringent regulatory authorities (SRAs) and the WHO prequalification program, up to providing full waivers for high priority paediatric drugs;
- Allowing compassionate use until drugs are registered; and
- Ending requirements for local clinical trials when sufficient PK and safety data exists, even when no innovator equivalent exists.

Action 24: Develop a toolkit to set standards and support accelerated research, development, and introduction of priority paediatric formulations.

UNICEF committed to**:**

Action 25: Work with countries on creating demand for paediatric HIV treatment services including generation of age disaggregated data to inform the better planning and supply forecasting.

Action 26: Through UNICEF supply Division, support rapid country adoption of new recommended regimens by including them on the UNICEF procurement services product lists and tenders for long term agreements.

Networks of PLHIV, Implementing Partners, and Faith-Based Organizations committed to

Action 27: Mobilize their networks and work with communities to help build treatment literacy, generate demand, and expand access to ARVs among children.

Action 28: Raising awareness in global fora about the unmet diagnostic and treatment needs of children with HIV.

Action 29: Promote uptake by mobilizing their networks of hospitals and community structures to distribute paediatric medicines in hard to reach places and in situations of conflict and crisis.

COLLABORATE on expedited development and introduction of paediatric products

Pharmaceutical companies committed to:

Action 30: Strengthen and expand collaboration to overcome intellectual property challenges and otherwise facilitate technology transfer and knowledge sharing that can promote faster paediatric formulation development, including on challenges like taste-masking.

All stakeholders committed to:

Action 31: Work together in a coordinated and transparent manner to ensure paediatric formulations are rapidly registered, introduced, and made widely available at an affordable cost in a maximum of high-burden countries.

Action 32: Identify alternative incentives and innovative financial mechanisms for the research, development and sustained supply of paediatric formulations, including advanced purchase commitments or other interventions.

Action 33: In addition to paediatric drugs and formulations in the pipeline, support the greater use of currently available WHO prequalified diagnostics and drugs in the WHO recommended regimens.

Implementing Partners committed to:

Action 34: Increase efforts to share information on the roll-out of new paediatric formulations, including lessons learned.

UNAIDS and PEPFAR as co-chairs of Start Free, Stay Free AIDS Free Framework committed to:

Action 35: Provide high-level political leadership and advocacy at global, country, and regional levels to scale-up access to paediatric HIV medications for children; to produce high-quality data to support implementation; and to provide country-level support to adoption of treatment options.

Action 36: Continue to convene and coordinate stakeholders at a high level, including the pharmaceutical industry; faith-based organizations; civil society service providers; national governments; multilateral partners; and other partners in the Start Free, Stay Free, AIDS Free Framework.

The Co-Chairs of the AIDS Free Working Group of the Start Free, Stay Free, AIDS Free framework committed to:

Action 37: Take responsibility for monitoring implementation of the Action Plan and holding actors to account, including monthly calls of principals, tracking progress towards milestones, and regularly communicating with participants about progress on their commitments and overall implementation of the Plan.

Action 38: Develop a set of milestones in 2018 to highlight progress on the Action Plan and establish opportunities for stakeholders to take on more specific commitments.

Action 39: GAP-f partners develop a work plan for finalization, roll-out and increasing demand for and accelerating access to 2-3 high priority drugs planned for approval in 2018.

Action 40: Continue to refine the Global Accelerator for Paediatric Formulations concept as a key component of the AIDS Free work stream, including by establishing leadership, roles and responsibilities, and a financing mechanism.

Action 41: Organize a follow-up meeting focused on diagnostics for children in Q1 2018.

Annex 1: Participating Organizations

Faith-based Organizations
Caritas Congo ASBL
Caritas Internationalis
Caritas Nigeria
Caritas Zimbabwe
Catholic Health Association of the United States
Catholic Relief Services
CMMB
Comunità Sant'Egidio
Medical Mission Institute Wuerzburg
Nyumbani
World Council of Churches - Ecumenical Advocacy Alliance
Governments
DRC - Programme national multisectoriel de lutte contre le sida
Republic of Zimbabwe - Ministry of Health and Child Care
Republic of Zimbabwe
Holy See
Cardinal Archbishop of Abuja
Dicastery for Promoting Integral Human Development
Holy See - Permanent Observer Mission to UNOG
International Organizations and Donors
Clinton Health Access Initiative
Drugs for Neglected Diseases *initiative* (DNDi)
Elizabeth Glaser Pediatric AIDS Foundation (EGPAF)
ELMA
ICAP, Columbia University
Istituto Superiore della Sanità
Medicines Patent Pool
MSF
PEPFAR
The Global Fund to Fight AIDS, TB and Malaria
The Global Network of People Living with HIV
UNAIDS
UNICEF
UNITAID
University of Roma Tor Vergata - Bambino Gesù Hospital
WHO
Pharmaceutical and Diagnostics Companies
Abbot/Alere
Becton-Dickinson
Cepheid
Cipla
Diagnostics for the Real World Ltd
Gilead Sciences, Inc.
Hetero Labs Ltd
Johnson & Johnson
Merck Sharp and Dome
Mylan
ViiV Healthcare
Regulators
US Food and Drug Administration

Annex 2: Individual Commitments

In addition to their support for the commitments in the Action Plan, several stakeholders participating in the High-Level Discussion made individual commitments, each of which made a significant contribution to the goals of the meeting. They include the following:

1. The US FDA committed to a number of adjustments to the regulatory approval process for paediatric formulations and to make them public on World AIDS Day:
    - Paediatric formulation development should begin soon after adult Phase 2-b trials and dosing selection;
    - Adolescents should be included in initial registrational efficacy (Phase 3) trials in adults or adolescent trials should be conducted in parallel with adults;
    - Studies of drugs across the paediatric spectrum of ages/weights (at least down to age 4 weeks) should be conducted in parallel rather than in series (unless a particular product has a specific safety or drug disposition factor that warrants a different approach).
    - Drug development studies in children should be based on weight rather than age and should align with the WHO weight bands.
2. PEPFAR committed to work with countries on a system of shared data and rotating locations for implementation studies; to develop a proposal for further expediting the regulatory approval process; and to fund the procurement of only optimal paediatric ARVs.
3. CHAI will commit full-time staff to assist EGPAF, WHO, PEPFAR, UNITAID and others to develop, coordinate and implement a detailed work plan to achieve the goals of the initiative; to assist with reaching agreements with companies, governments, donors and regulators to accelerate the introduction of optimal formulations and diagnostics for children and adolescents both short term and long term; and to work with governments and faith based organizations to scale up identification and treatment of HIV infected children and adolescents in the target countries.
4. Gilead committed to having clinical data ready for a low-dose TAF based regimen for children 2-12 years by late 2018/early 2019.
5. Merck & Co., Inc., is committed to make pediatric Raltegravir available at no profit in low income, least developed countries and across Sub-saharan African countries until generics are available.
6. ViiV Healthcare committed to deploy people, resources and technical expertise to speed up as much as possible the generation of data for regulatory approval of medicines for children living with HIV, including the ongoing development of Dolutegravir for children.
7. ViiV Healthcare committed to make paediatric Dolutegravir available at cost of production in low income countries, least developed countries and across Sub-Saharan African countries until generics are available.
8. Cipla committed to scale-up production of Lopinavir/Ritonavir (LPVr) pellets to 30,000 bottles per month in 2018 and to submitting the new “4-in-1” (ABC/3TC/LPV/r) pellets in 2018.
9. Mylan committed to submitting LPV/r granules for regulatory approval in 2017; “4-in-1” (ABC/3TC/LPV/r) granules in 2018; and a paediatric ABC/3TC/DTG formulation in 2019, subject to the WHO providing paediatric DTG dosing guidance in early 2018.
10. The Global Network of People living with HIV (GNP+) committed to mobilize their networks, in particular women living with HIV, to increase demand generation, advocacy, and monitoring to increase access to treatment for children living with HIV.
11. Cardinal Turkson committed the Catholic Church to mobilize their networks of both hospitals, and community structures to distribute paediatric medicines in hard to reach places and in situations of conflict and crisis.
12. Unitaid will continue to invest in development and rapid introduction of priority products for infants and children.
13. The Medicines Patent Pool (MPP) commits to facilitating access to the best available medicines for children. Specifically, the MPP will continue to work with patent holders to in-license paediatric drugs as prioritized by the WHO/PADO, and to sublicense to generic manufacturers to ensure that

appropriate formulations are rapidly developed, registered and made available in as many developing countries as possible.