

Status Report on the Action Plan for Scaling Up Early Diagnosis and Treatment of Children and Adolescents (“Rome Action Plan”)
AIDS Free Working Group Co-Chairs

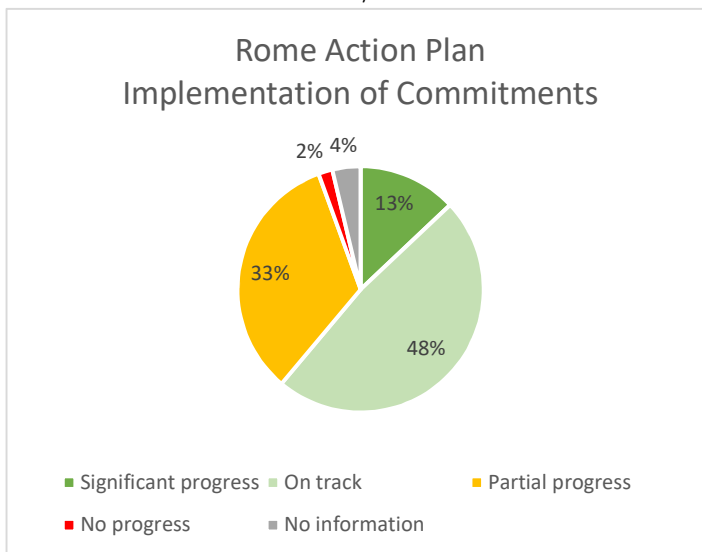
December 2018

Overview

In November 2017, stakeholders concerned about accelerating access to optimal HIV treatment for children met in the Vatican and adopted by consensus the Action Plan for Scaling Up Early Diagnosis and Treatment of Children and Adolescents (“Rome Action Plan”), composed of 41 cross-cutting commitments and 11 commitments by individual actors. As the document was based on numerous previous consultations with stakeholders and included a constructive accountability mechanism, there has been a positive spirit of collaboration regarding its implementation. Indeed, an assessment of stakeholders’ efforts over the past year by the AIDS Free Working Group co-chairs show meaningful progress across its three central themes – focus, accelerate, and collaborate.

The most notable efforts have been in the areas of “focus” and “collaboration,” with enhanced dissemination of information about which pediatric ARV formulations should be prioritized and how helping all actors understand where to focus their R&D and introduction efforts. As well, many stakeholders are actively working together to promote faster and broader uptake of new drugs and formulations currently in the pipeline, and to build greater political support for increasing the proportion of children living with HIV on treatment. Progress on commitments made under the “acceleration” header has been mixed, however, especially on the finalization and uptake of drugs on the Paediatric ARV Drug Optimization (PADO) list of priority formulations.

The AIDS Free Working Group co-chairs’ evaluation shows there has been significant progress on around 13% of all the action points and commitments, signifying vital activities that would likely not have happened at all or to the same extent without the Rome Action Plan and/or those that have been fully implemented. Around 48% are on track, indicating commitments being implemented at a good pace, many of which were ongoing before the Action Plan was agreed though activities may have been enhanced or made more visible as a result of the Vatican process. In 33% of the cases, often commitments composed of multiple elements, progress may have been made on some parts, but not others. Fortunately, there are relatively few actions where no clear progress can be observed (2%) or for which no reports have been provided (4%). An overview of activities in the three themes of the Action Plan is provided below.



1. Focus

Since the High-Level Consultation at the Vatican in November 2017, stakeholders have amplified efforts to clarify and heighten awareness about the highest priority ARV formulations and the urgent need to focus research, development, and uptake efforts on those particular ARVs. These priority ARVs for children are set out by the Paediatric ARV Drug Optimization (PADO) group, led by WHO, which meets to review the list every year with interim reviews to inform its implementation. In order to increase transparency around its conclusions, PADO members held a webinar for industry and regulators in February 2018 about the decisions taken in the December 2017 PADO3 review. The next PADO meeting (PADO4) is planned for 10-12 December 2018, and the webinar for industry and regulators planned for 19 December. An update of the WHO Expression of Interest (EOI) list to take into account the PADO review will occur immediately afterwards. **[Action 1]**

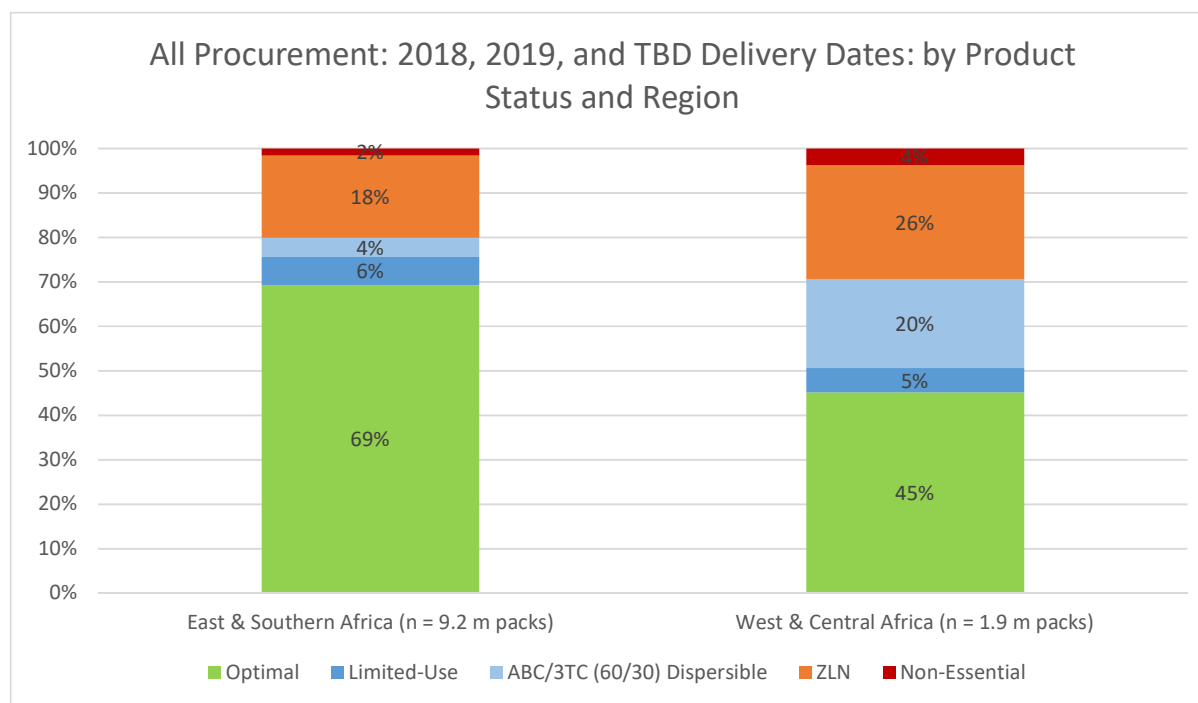
WHO has also revised treatment guidelines in July 2018, which include more potent regimens for neonates and children. Since then, WHO, in collaboration with UNICEF and APWG, has held several webinars to disseminate the new guidelines. **[Action 2]** The Paediatric ARVs Working Group (PAWG) has continued to meet every two months and developed dosing guidance for the WHO guideline update. Conversations are ongoing on the suggested dosing and ratio for DTG/TAF/XTC, one of the PADO list formulations. **[Action 3]** Key stakeholders met in June to update the Optimal Paediatric ARV Formulary and Limited Use List to support product selection, and they were included in the AIDS FREE toolkit (see below) for broad dissemination together with a policy brief on implementation considerations issued to support national transition. Submissions for modification of the Essential Medicines List (EML) in line with the optimal formulary is planned for early December 2018. **[Action 4]** Toolkits on Research and Development of Paediatric Antiretroviral Drugs and Formulations (PAWG) and Accelerating Progress in Testing and Treatment for Children and Adolescents with HIV (AIDS FREE toolkit) were launched in July. Information on PADO priorities and the Rome Action Plan were communicated to IMPAACT and PENTA members, and the research networks have been actively collaborating to accelerate completion of the Dolutegravir (DTG) plan **[Action 5]**.

Concerted efforts are ongoing to finish development or introduce 4 of the 8 mid-term paediatric ARV priorities set out in PADO3 (DRVr, RAL, DTG single, DTG/3TC/ABC), with delays in getting dosing information for DTG and the unavailability of paediatric F/TAF¹ slowing progress on other formulations. As well, two formulations (LPV/r 4-in-1 and ABC/3TC/EFV) on a previous PADO list are nearing completion with support from the Paediatric HIV Treatment Initiative (PHTI) members DNDi and MPP. Information is lacking on efforts to prioritize longer-term PADO products such as long acting oral/injectable drugs or neutralizing antibodies for children in R&D plans **[Action 6]**, or for stringent regulatory authorities (SRAs) to prioritize PSPs and PIPs for PADO formulations over lower priority drugs. **[Action 7]**

Donors have been proactively supporting development and access to PADO drugs. For example, Unitaid has continued its support to the innovative CHAI Optimizing ARVs project, and in July 2018, CHAI announced that it will work with Macleods and Mylan on expedited development of DTG 10 mg scored in close collaboration with ViiV. Unitaid also continued to support the development of other paediatric ARVs via the PHTI. PEPFAR will provide support for a monitored introduction of Raltegravir granules for neonates in Eswatini and to develop educational and training materials that can be used in other countries, in partnership with Merck and EGPAF. **[Action 8]** On the procurement side, the PEPFAR COP18 guidance emphasized that there would be no funding for non-optimal ARVs, including no nevirapine (NVP) for older children, and the Global Fund will not allow procurement of medicines unless they are in the current national, institutional and/or WHO Standard Treatment Guidelines and/or Essential Medicines Lists. **[Action 9]** The ARV Procurement WG continues to monitor and encourage procurement of optimal formulations and to promote reliable consolidation of orders, supported in 2018 by the launch of a new website. **[Action 10]** The chart below shows APWG's analysis of recent

¹ Studies for TAF-based regimen in children >6Y completed, but the combination tested are not PADO-recommended formulations and will not enable full approval of F-TAF to cover different age and weights with boosted and unboosted regimens

procurement by those countries for which procurement is done or partially done via one of the APWG consortium members.²



2. Accelerate

The most notable move to speed up the research, development, and introduction of optimal ARVs was FDA’s commitment to accept several new elements within pediatric ARV development plans that could accelerate completion of pediatric plans. This verbal commitment at the Vatican was reaffirmed in a January 2018 letter to the United States Global AIDS Coordinator, and in May, the steps were again outlined in FDA’s draft guidance for industry entitled [“Pediatric HIV Infection: Drug Development for Treatment.”](#) The European Medicines Agency (EMA) also confirmed alignment to similar principles during a Paediatric Committee (PDCO) meeting in May 2018, but it has less flexibility about making this clarification public. EMA has also prepared an [Action Plan on Paediatrics](#) to improve the implementation of its Paediatric Regulations, though many items are not planned until 2020. [Action 20, FDA commitment].

Some innovator companies have reported taking steps to put in place the compressed timelines in the research and development of pediatric ARVs schedules as called for in the Rome Action Plan and now accepted by FDA and EMA. ViiV and Gilead have reported that they are conducting trials for adolescents at the same time as adults (e.g., for DTG and E/C/F/TAF and F/TAF, respectively) [Action 14], and some compression of age groups has occurred in trials for DTG and cabotegravir, with P1093 and ODYSSEY using weight bands-based dosing and concurrent age groups. Gilead reports working with FDA and EMA on its plans to use weight bands and to compress all age groups into parallel or overlapping trials in future PSPs and PIPs for ARVs [Actions 15 & 19.] ViiV reports that assessing acceptability and palatability of formulations in high burden countries is a key consideration at the start of paediatric formulation development, and Gilead committed to assessing acceptability by expert taste testers within the context of its pediatric studies and to make data public once it

² Given the recent demotion of ABC/3TC (60/30 mg) dispersible tablets to the non-essential list (due to a better formulation of ABC/3TC), it was shown as a separate product as it constituted a large proportion of non-essential procurement in African countries. AZT/3TC/NVP (ZLN) is still used in many countries for <3Y while awaiting availability of a more optimal formulation.

has been generated for all pediatric formulations studied. [Action 16] The PAWG continues to provide advice to SRAs and innovators on pediatric drug development plans. [Action 11] Yet while Gilead did consult with PAWG on its pediatric development plans for F/TAF in spring 2018, it did not appear to take on board PAWG’s advice to prioritize the development of F/TAF for all children over other formulations. [Action 17] More generally, ViiV and Gilead report heightened resources and cross-departmental focus on pediatric ARVs with potential to boost their longer-term research and development efforts. To support industry’s intensified work on optimal ARVs, WHO in collaboration with Unitaid, IMPAACT, PENTA-ID and other GAP-f Partners developed an extensive toolkit for research and development of paediatric antiretroviral drugs and formulations, launched at AIDS 2018 in July and followed by a series of 6 dissemination webinars in Q4 2018. [Action 24]

A central element of the Rome Action Plan was to accelerate development and introduction of pediatric ARVs currently in the pipeline, which have seen repeated delays in recent years. Overall, the development of most PADO drugs has not been accelerated to the extent hoped for under this initiative. While some plans for drug submission and scale-up are on track, others are delayed by several months, and one is 2-3 years behind schedule (see table below). It is certainly complicated to predict such timelines, but in some cases it appears that delays might have been lessened if the companies had made more effort to enroll children faster in trials or to provide the formulations needed for trials more quickly. In one case delays appear due to a prioritization of non-PADO formulations over the PADO recommended regimen [Action 18]

Status of Pharmaceutical companies’ Commitments on Formulation Development

Pharmaceutical company	Commitment	Status
Cipla	Scale-up production of Lopinavir/Ritonavir (LPV/r) pellets to 30,000 bottles per month in 2018 and submit the new “4-in-1” (ABC/3TC/LPV/r) pellets in 2018.	Request for modified production method of LPV/r to enable higher production levels was approved by FDA in June 2018. Capacity now at 60,000 bottles/month. 4-in-1 granules: expect to file dossier with FDA as soon as possible after December 2018 NDA meeting.
Gilead	Have clinical data ready for a low-dose TAF based regimen for children 2-12 years by late 2018/early 2019.	Concerning the only TAF regimen on the PADO list (F/TAF), Gilead will leverage data from the study of other pediatric ARVs containing F/TAF. The ≥25 kg formulation is now approved for unboosted indication. Submission for boosted indication expected for ≥25 kg and 14-<25 kg in 2020. For <14 kg, filing expected for unboosted in 2020 and boosted in 2021.
Mylan	Submit 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.	Submitted LPV/r granules for PQ in Dec. 2017; to ERP in Jan. 2018. Received FDA tentative approval in August 2018 – now scaling up production. Plans submission of 4-in-1 granules to PQ and FDA in Q2 2019. ABC/3TC/DTG not expected until Q4 2020 at the earliest as still waiting for DTG dosing guidance by the end of 2018.
ViiV	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	Plans to submit DTG for children >3kg (5mg and 50mg) in late 2019. Met with FDA in June to discuss next steps. In parallel, CHAI announced in July 2018 that it will work with Macleods and Mylan on expedited development of generic versions of DTG 10 mg scored in close collaboration with ViiV and with support from Unitaid’s Optimal ARV grant.

Several commitments aim to see accelerated in-country registration, introduction, and uptake of these new formulations once they become available. While the Paediatric Regulatory Network to facilitate national registration of specific products has not yet been reestablished by WHO, other efforts are underway to increase use of the collaborative registration procedures (CRP), especially in the AIDS FREE priority countries. In particular, PEPFAR and WHO announced at the end of November a pilot program to implement CRP based on data provided to and assessed by FDA. **[Actions 12 & 23]** Among donors, PEPFAR, in addition to providing funds to implementing partners to support introduction of new drug regimens, has been working directly with Merck, ViiV, J&J on their plans to bridge supply of optimal paediatric ARV products in PEPFAR-supported HIV programs until they are available from other sources. **[Action 21]** In line with this effort, these three companies have confirmed their intent to provide RAL, DTG, and Darunavir/ritonavir (DRV/r) at cost of production until generic versions are available, and Gilead pledged to make paediatric formulations of its HIV drugs available at access pricing. **[ViiV, Merck individual commitments]**

In order to support wider uptake of paediatric formulations in Western and Central Africa, UNICEF and partners hosted a large multicountry workshop to promote adoption of family based index case testing policies, followed by targeted technical assistance visits to countries. **[Action 25]** In addition, UNICEF has placed on its products list of ARV formulations all paediatric formulations included in the Optimal formulary, and UNICEF SD continues to advocate for countries to procure optimal paediatric formulations. **[Action 26]** In other efforts to expand access to paediatric treatment, GNP+ has taken a number of steps to increase awareness and advocacy on access to paediatric ARVs with the community of people living with HIV and treatment access advocates, such as by including access to paediatric DTG in its series of webinars in 2018 on treatment updates and a survey to PLHIV in the spring. **[Action 27 and GNP+ commitment]**.

IPs and faith-based organizations (FBOs) are continuing to raise awareness on the need to expand access to optimal paediatric ARVs in various fora and are working to support ARV distribution in hard to reach places and situation of conflict and crisis. For example, under the framework of the PEPFAR-UNAIDS FBO Initiative, Caritas Internationalis has been leading a project in Nigeria and DRC to mobilize faith-based groups and religious leaders on paediatric case finding and treatment access, as well as to build capacity on paediatric HIV in faith-based health facilities. As well, the World Council of Churches-Ecumenical Advocacy Alliance has been leading numerous interfaith campaigns, workshops, and trainings on paediatric HIV aimed at reducing stigma, encouraging leadership by faith leaders, and promoting advocacy by religious leaders and young people, including through a children's letter writing campaign to national leaders on access to better ARVs in November 2018. **[Actions 28 & 29, and Catholic Church commitment]**

3. Collaborate

Finally, the Rome Action Plan has helped spark or maintain close collaboration among public, private, and non-governmental actors on paediatric ARVs. GAP-f partners are working individually and together to facilitate rapid registration and uptake of optimal drugs and formulations in the pipeline (LPV/r, 4-in-1, DTG, RAL). For example, in support of the Unitaid-supported Optimal ARV project, GAP-f partners have been working with ViiV and regulatory authorities to determine the best regulatory pathways for paediatric DTG (10 mg scored and 50 mg scored tablets) and ways to accelerate registration and introduction of DTG at country level. WHO is facilitating the provision of coordinated support to enable rapid transition to optimal products in the 21 priority countries and has convened several dedicated TWG meetings where transition plans to optimal formulations are being developed. The Paediatric HIV Treatment Initiative (PHTI) partners met in June and October to discuss collaboration on the registration, introduction, forecasting and roll-out of formulations expected to become available in 2019. An additional consultation was convened by WHO in September to promote harmonization and consolidation of forecasting efforts. DNDi is collaborating with EGPAF and ICAP to prepare rapid roll-out of the new 4-in-1 formulation. **[Actions 30-33]** Resulting lessons learned from this collaboration, as well as the

introduction of RAL in Eswatini noted above, will be shared with other countries preparing to introduce those drugs [Action 34].

The collaboration among CHAI and ViiV (with support from Unitaid) to expedite development of generic versions of DTG is especially remarkable as it will allow for early technology transfer to two generic companies and use of an innovative financial mechanism. ViiV reports ongoing work on an agreement with other pharmaceutical companies to facilitate technology transfer and knowledge sharing. Innovative financial mechanisms are also being explored via the CHAI Optimal ARV project funded by Unitaid and currently being refined for inclusion in the GAP-f business plan. The International AIDS Society Industry Liaison Forum published a policy brief describing how advance procurement could help incentivize the development of priority paediatric drug formulations [Actions 30 & 32]

PEPFAR, UNAIDS, UNICEF, WHO and others continue their efforts to keep pediatric treatment on global, regional, and national political agendas, to provide political leadership and advocacy, and to convene stakeholders at high levels. UNAIDS' global AIDS update report launched in July 2018 included information on reaching AIDS Free targets, and the annual Start Free, Stay Free, AIDS Free report expected in January 2019 will also highlight pediatric treatment progress and challenges. UNAIDS continues to support the Free to Shine Campaign, which includes advocacy on pediatric treatment, and is working with countries on setting pediatric treatment targets within NSPs. PEPFAR included pediatric treatment targets in all 2018 COPs. [Actions 35 & 36]

GAP-f partners are working on plans to finalize, roll-out, increase demand for, and accelerate access to 3-4 drugs (LPV/r, 4-in-1, DTG, RAL) as well as on a product portfolio to include in the Business Plan. [Action 39] GAP-f was launched at AIDS2018, and the concept for GAP-f was laid out in an article in the Lancet, "Catalysing the development and introduction of paediatric drug formulations for children living with HIV: a new global collaborative framework for action partners." GAP-f partners are finalizing a new business plan and are working on identifying innovative financing mechanisms to support the R&D of pediatric ARVs. [Action 40]

Finally, the Rome Action Plan called for a follow-on meeting on diagnostics as there was insufficient time at the 2017 meeting to have detailed discussions on this key element of the testing and treatment equation. This action point led to the organization of a series of multilateral and bilateral consultations on pediatric HIV case-finding and diagnostics, including two convened by PEPFAR. Such meetings laid a solid groundwork for the High Level Dialogue on pediatric diagnostics and treatment in December 2018. [Action 41]

Conclusion

The Co-chairs recognize this brief overview cannot do justice to the multitude of activities that have stemmed from, or otherwise been amplified by the Rome Action Plan and the overall Vatican initiative. But it does demonstrate that the Rome Action Plan has inspired a wide variety of stakeholders to step up their efforts on pediatric ARVs and to collaborate with others to seek further progress, all with the aim of delivering on the commitments made at the Vatican and improving outcomes for children. Indeed, partnership and transparency have been the hallmarks of the Plan's development and implementation, enhanced by the AFWG Co-chairs' regular monitoring and communications. [Actions 37-38]

At the same time, progress has been far from uniform, and there are still many areas that require intensified efforts, especially regarding the finalization of new optimal drugs that have been pending for many years. The Vatican dialogue has never tried to mask the complexity and the costs associated with pediatric drug and formulation development, but it did set out a series of concrete steps with potential to accelerate the process as much as feasible. Full, expedited implementation of those steps, with continued openness about challenges and collaborative efforts to find solutions together, is therefore of utmost importance. The AFWG Co-chairs will continue to monitor such efforts and stand ready to support any requests to address remaining challenges.