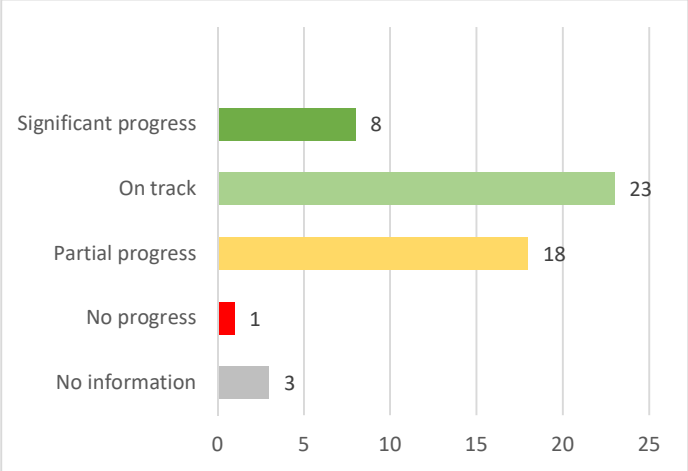
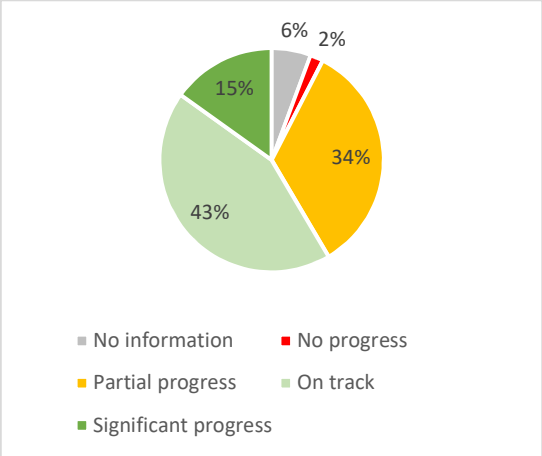
Rome Action Plan – Status Report
October 2018

Summary: The Rome Action Plan has led to solid progress in each of the key areas – focus, accelerate, and collaborate. Under "Focus" and "Collaboration," we see perhaps the most progress, with widespread dissemination of priority pediatric ARV formulations helping all actors understand where to focus R&D and introduction efforts, and many stakeholders actively working together to promote rapid and broader uptake of new drugs/formulations. Progress on "Acceleration" has been mixed, however, with FDA's step to promote a compressed development timetable and the CHAI-ViiV collaboration to accelerate generic DTG development being great steps forward, but other development of most PADO drugs not being accelerated to the extend hoped for under this initiative.

While many of the commitments were aligned with ongoing activities, some efforts are now more visible, some have been amplified, and some are indeed new and due to the Rome Action Plan. We have classified progress in 5 groups – from those with truly noteworthy progress down to those for which we have no update. While the actions and commitments are often multi-faceted and not always SMART, our assessment is that of all the action points and commitments, around 15% have made significant progress, 43% are on track, 34% have made partial progress, 2% have had no progress, and 6% we lack information.





There have been notable developments in about 15% of the commitments, including:

- FDA's clarification of regulatory requirements to accelerate completion of pediatric plans – in a letter to Amb. Birx and in draft guidelines to industry. EMA has confirmed alignment during its recent PDCO meeting, but has less flexibility about making this clarification public.
- Clear communication on PADO priorities to industry, research networks, and other stakeholders. The next PADO is planned for December, with a webinar for industry the following week.
- 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.
- WHO 2018 treatment guideline update, launched in July, included more potent regimens for neonates and children, and the Optimal formulary and limited use list to support transition and product selection was also revised.
- A wide group of stakeholders, particularly PHTI partners with Unitaid support, are working individually and in collaboration to prepare for the rapid introduction of new pediatric formulations

- The AIDS Free WG co-chairs are finalizing organization of a high-level meeting in December on Pediatric Treatment and Diagnostics.

Progress is on-track in about 43% of the commitments, including:

- Develop, scale-up production of, and introduce some optimal drugs/formulations, supported in some cases with new support from donors, and to limit procurement to those on the optimal formulary. The collaboration among CHAI and ViiV (with support from Unitaid) to expedite development of generic versions of DTG is especially remarkable as is will allow for early technology transfer to two generic companies and use an innovative regulatory pathway.
- Keep pediatric treatment on the global, regional, and national political agendas, through work by PEPFAR, UNAIDS, UNICEF, WHO and others
- GAP-f was launched at AIDS2018 and a business plan is being finalized. GAP-f partners are working on identifying innovative financing mechanisms to support the R&D of pediatric ARVs.
- GNP+ has taken a number of steps to increase awareness and advocacy on access to pediatric ARVs with the community of people living with HIV and treatment access advocates.

Partial or limited progress has been observed in 36% of the commitments, including:

- Development has been delayed by 6-12 months or more for several optimal drugs/formulations. We know it is not easy to predict such timelines, but in some cases we understand that delays might have been lessened if the companies had made more effort to enroll children faster in trials or to provide more quickly the formulations needed for trials. As accelerated availability of these new medicines is at the heart of the Vatican initiative, we hope to see greater efforts by all to reduce such delays.
- Promoting greater use of collaborative procedures (CRP or sub-regional) to expedite NRA approval. We understand that there are ongoing discussions to expand the use of CRP – to additional SRAs and countries, and hope there can be positive news at the Vatican meeting.

We currently do not have information on efforts most pharmaceutical companies are making to compress timelines in the research and development of pediatric ARVs. ViiV reported on a few steps they are taking, such as testing adolescents in parallel to adults for Dolutegravir, but we would like to hear more from all actors, including whether they are influenced by FDA's clarifications. Nor do we have clear information on steps to expedite regulatory review of priority pediatric drugs by SRAs, PQ, and NRAs.

The Rome Action Plan was based on a series of open dialogues among a wide set of partners, many of whom committed to even more steps than was originally planned. Collaboration and transparency have been the hallmarks of its development and implementation. We welcome the updates you have been sending to keep us all informed on progress. Please keep them coming so we can keep up the momentum – some stakeholders are communicating more information, more frequently than others, but we rely on regular, up to date information from all stakeholders to ensure this Plan is successfully implemented.

Significant progress

- WHO – Actions 1-2: Revised WHO treatment guidelines with inclusion of more potent regimens for neonates and children were released in July. Several webinars for dissemination have already occurred in collaboration with UNICEF and APWG. PADO4 is being planned for December 10th to 12th, with webinar for dissemination to industry and regulators scheduled for Dec 19th. Update of EOI will occur immediately after.
- WHO – Action 4: The optimal pediatric formulary and limited used list were revised in June and included in the AIDS FREE toolkit for broad dissemination. A policy brief on implementation considerations was

issued to support national transition. Submission for modification of EML in line with the optimal formulary will happen by the end of November.

- SRAs – Action 20 / FDA commitment: In May, the FDA issued draft guidance for industry entitled ''Pediatric HIV Infection: Drug Development for Treatment" including acceptance of accelerated steps when evaluating paediatric development plans and reviewing drug applications. In response to WHO request, EMA's PDCO endorsed a similar set of principles at a meeting in late May, and has prepared an Action Plan on Paediatrics to improve the implementation of the Paediatric Regulation.
- IPs and FBOs – Action 22: EGPAF and CHAI beginning preparations for introduction of DTG (CHAI and EGPAF) and RAL (EGPAF), including production of a DTG introduction toolkit. CHAI announced in July 2018 that it will work with Macleods and Mylan on expedited development of DTG 10 mg scored in close collaboration with ViiV and with support from Unitaid's Optimal ARV Project. GAP-f partners have been discussing with ViiV and regulatory authorities to determine the best regulatory pathways for pediatric DTG (10 mg scored and 50 mg scored tablets) and ways to accelerate registration and introduction of DTG and RAL at country level.
- GAP-f Partners – Action 24: Toolkit for research and development of paediatric antiretroviral drugs and formulations was launched at AIDS 2018 in July, followed by a series of 6 dissemination webinars Q4 2018.
- All – Action 31: GAP-f partners are working individually and collaboratively on rapid registration and uptake of drugs in the pipeline (LPV/r, 4-in-1, DTG, RAL). WHO is facilitating the provision of a coordinated support to enable rapid transition to optimal products in the 21 priority countries and convening dedicated TWG meetings where transition plans to optimal formulations are being developed (2 meetings have already occurred in Uganda and Tanzania, additional 8 are planned to happen by the end of the year). The Pediatric 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.
- AFWG Co-chairs – Action 41 –A high-level diagnostics meeting will take place December 6-7 in the Vatican. Several preparatory meetings have already taken place, including at AIDS 2018 in July.

On track

- WHO – Actions 3: PAWG has continued to meet every two months and developed dosing guidance for WHO guideline update. Ongoing conversation on dosing and ratio for DTG/TAF/XTC.
- Research networks – Action 5: PADO priorities and Rome Action plan communicated to IMPAACT and PENTA members in the spring with active collaboration to accelerate completion of DTG plan. IMPAACT and PENTA played role as key partners of Unitaid and WHO in developing the research and development toolkit including continuing to contribute to its dissemination
- Donors – Action 8: PEPFAR is working with IPs on support for monitored introduction of Raltegravir granules for neonates. PEPFAR has also been working directly with Merck, ViiV, J&J on their plans to bridge supply optimal pediatric ARV products in PEPFAR-supported HIV programs until they are available from other sources. Unitaid is supporting the CHAI Optimizing ARVs work on DTG and other pediatric ARVs through PHTI.
- Donors – Action 9: PEPFAR COP18 guidance emphasized no funding for non-optimal ARVs, such no NVP for older children. APWG partners continue to monitor and encourage procurement of optimal formulations
- WHO – Action 11: WHO sent letter to EMA on technical opinions on PIPs, which were also shared with FDA.
- Research networks – Action 19: P1093 and ODYSSEY using weight bands-based dosing and concurrent age groups

- Donors – Action 21: PEPFAR provides funds to implementing partners to support introduction of new drug regimens. Unitaid supports acceleration of the development and introduction of priority products, including facilitating rapid introduction of paediatric DTG in early adopting countries, leveraging the Optimal ARV Project in collaboration with CHAI. PEPFAR is working with Merck and other partners on a plan for assisted introduction of RAL granules for neonates and to develop educational and training materials.
- UNICEF - Action 25: In collaboration with USG (USAID, CDC & PEPFAR), UNAIDS and WHO, UNICEF is planning multi-country meetings for the WCA & ECA for early 2019 to build capacity in countries for availability and use of age, sex and geographic disaggregated data for planning and programming.
- PLHIV, IPs, FBOs – Action 28: Ongoing awareness raising on pediatric ARVs in various fora
- PLHIV, IPs, FBOs – Action 29: Ongoing efforts on ARV distribution in hard to reach places and situation of conflict/crisis
- All – Action 33: GAP-f, APWG continue to support use of currently available pediatric drugs
- UNAIDS & PEPFAR – Actions 35&36: Ongoing work to provide political leadership and advocacy, convene stakeholders at high levels. The global AIDS update report was launched in July 2018 and included information on reaching AIDS Free targets. The annual 3 Frees report is expected in Q4. UNAIDS continues to support the Free to Shine Campaign, which includes advocacy on pediatric treatment.
- AFWG Co-chairs – Actions 37-38: Regular monitoring of Action Plan implementation with milestones set
- AFWG Co-chairs – Action 39: GAP-f partners are working on plans to roll-out 2-3 drugs (LPV/r, 4-in-1, DTG, RAL) as well as on a product portfolio to include in the Business Plan, to be finalized by the next high level meeting.
- AFWG Co-chairs/GAP-f Partners – Action 40: 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
- Merck: Confirmed to PEPFAR it will make RAL available at access price and is working on an introduction pilot
- ViiV: Confirmed to PEPFAR it will make DTG available at access price.
- Cipla – Request for modified production method of LPV/r to enable higher production levels was approved by FDA. 4 in 1 granules: expect to file dossier with FDA in with BE data in Q3 and clinical data in December 2018.
- Catholic church: Ongoing work to mobilize its networks to distribute paediatric medicines in hard to reach places and in situations of conflict and crisis
- MPP: Ongoing work within PHTI to bring RAL and ALE to market
- GNP+ has taken a number of steps to increase awareness and advocacy on access to pediatric ARVs with the community of people living with HIV and treatment access advocates.

Partial progress

- IPs – Action 10: ARV Procurement WG continues to promote reliable forecasts and consolidation of orders, including through a new website: https://www.arvprocurementworkinggroup.org/, but no information from IPs on revision of national procurement plans
- WHO – Action 12: Working with EMP on facilitation of national registration and in-country registration of specific products.
- Pharma – Action 13: ViiV will further increase resources and focus on paediatrics, including by appointing a Paediatric Medicines Development Lead (MDL) who will work across of ViiV's R&D portfolio to bolster the portfolio approach to ViiV's efforts in paediatric ARV development

- Pharma – Action 14: ViiV conducted DTG trials for adolescents 12Y >40kg in parallel with Phase 3 clinical development for adults so they could be part of first licensing.
- Pharma – Action 15: Some compression of age groups has occurred in trials for DTG and cabotegravir.
- Pharma – Action 16. ViiV reports that assessing acceptability and palatability of formulations in high burden countries is a key consideration at the start of paediatric formulation development.
- Pharma – Action 18: While some plans for drug submission and scale-up are on track, others have been delayed by 6-12 months or more for several drugs, and one is completely off track.
- GAP-f – Action 23: PEPFAR and WHO PQ have discussed how to implement CRP based on SRA approval, conversation ongoing. Countries among the AIDS FREE priority countries who are not included in CRP list were identified.
- UNICEF - Action 26: All paediatric formulations included in the Optimal AVR formulary needed to provide WHO recommended preferred and alternative first- and second- line regimens for all children have been placed on UNICEFs products list of ARV formulations, and UNICEF SD continues to advocate for countries to procure optimal paediatric formulations.
- PLHIV, IPs, FBOs – Action 27: GNP+ launched a webinar series on treatment updates, with the first one in March including access to paediatric versions of DTG was discussed.
- Pharma – Action 30: ViiV reports ongoing work on an agreement with other pharmaceutical companies, but no public information available yet on tech transfer and knowledge-sharing. In the context of CHAI's Optimal ARV project, it transferred technology to Macleods and Mylan for the expedited development of generic DTG 10mg scored.
- All - Action 32: Innovative financial mechanism being explored via the CHAI Optimal ARV project funded by Unitaid and currently being refined for inclusion in the GAPf business plan.
- Pharma - Action 18: ViiV plans to submit DTG for children down to 3kg in late 2019. Cipla and Mylan took steps on LPV/r. Delayed progress on Mylan's 4-in-1 and very slow progress on F/TAF
- IP – Action 34: DNDi shares information on introduction of LPV/r pellets
- PEPFAR: PEPFAR has developed a website that makes program data available for review and analysis. PEPFAR is developing a mechanism for addressing requests from external stakeholders and partners for more detailed program data to use in important analyses. PEPFAR has not yet developed sites for implementation studies.
- CHAI – Announced in July 2018 that it will work with Macleods and Mylan on expedited development of DTG 10 mg scored in close collaboration with ViiV and with support from Unitaid's Optimal ARV grant.
- Mylan – 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 in December 2018, and to FDA in Q2 2019. ABC/3TC/DTG not expected until Q2 2020 as still waiting for DTG dosing guidance by the end of 2018.
- ViiV – Added high level staff and resources devoted to pediatric R&D, but development of DTG has been delayed. Formulations for children >3kg (5mg and 50mg) are now expected to be submitted to FDA in late 2019. Met with FDA in June to discuss next steps.

Progress needed

- Gilead: 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.

No Information

- Pharma – Actions 6, 17: No information on efforts to prioritize PADO products in R&D plans and engage with PAWG on PIP/PSPs, recommended dosing and ratios for FDC development (Note: no info on Actions 13- 16 from most companies)
- SRAs – Action 7: GAP-f members developing proposals to communicate to FDA and EMA on priority review of PADO-related PSPs and PIPs, but no information from SRAs on efforts to prioritize review of PSPs and PIPs for PADO formulations