CONCLUSION

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1. CONTEXT

This toolkit is part of a wider global initiative to raise awareness of the historical and ongoing delays in developing and commercializing HIV drugs in formulations suitable for children and adolescents and to find innovative ways to accelerate this process *(1,2)*. Efforts in recent years have focused on promoting intersectoral collaboration, giving priority to the most needed formulations for children, establishing a formulary of existing drug formulations required for optimal treatment of children and coordinating the procurement of antiretroviral (ARV) drugs in low- and middle-income countries *(2)*.

Building on these ongoing initiatives, this toolkit brings together the knowledge and experience of key experts on HIV to suggest pragmatic ways to further accelerate the drug development time scale.

2. SUMMARY OF KEY CONSIDERATIONS

The key considerations arising from this toolkit centre around:

- earlier planning and coordination to facilitate the design and conduct of key research studies;
- including key population groups (young children, adolescents and pregnant and breastfeeding women) in the research process;
- more efficiently using the available data to fill knowledge gaps and minimize the need for additional studies; and
- increasing collaboration and coordination among key stakeholders throughout the key stages of drug development.

2.1 Earlier planning and acceleration of research studies

This toolkit provides many examples of ways to accelerate the development of drugs for children by establishing communication channels between key stakeholders early in the drug development process and accelerating appropriately designed research studies, which should include key population groups from the start.

- Early communication between all stakeholders is needed to facilitate timely planning of studies of novel drugs involving children and pregnant women.
- The development of age-appropriate formulations suitable for low- and middle-income countries should be initiated as soon as reassuring safety and efficacy data are available from Phase II trials involving adults.
- For this to happen, clinical trials, pharmacokinetic studies and acceptability studies involving children should be designed alongside research studies involving adults and in close collaboration with regulatory authorities to establish what data are needed early on.
- Community engagement should occur as early as possible in designing clinical trials and acceptability studies. Community groups should be engaged throughout the process of drug development, including during the planning and design of clinical trials involving children.

- Target product profiles should be developed early in the drug development process, to enable formulations to be adapted if needed.
- Specific country regulatory requirements need to be considered early on to avoid additional hurdles and obstacles to importation and in-country approvals.
- Generic drug manufacturers also need to be involved early in the drug development process.

2.2 Including pregnant women, children and adolescents in clinical trials

A more inclusive approach to clinical trial eligibility should be embraced, with more widespread inclusion of pregnant and breastfeeding women, adolescents and children of all ages, including those with coinfections.

- Novel drugs with well established safety and metabolic profiles should be evaluated concurrently across weight and age ranges, taking advantage of pharmacodynamic and pharmacokinetic modelling to estimate starting doses. The age groups or weight bands should be staggered only if there is a specific safety concern.
- Adolescents should be included in clinical trials involving adults, since they usually use the formulations and doses for adults, and no major differences in safety and efficacy are expected compared with adults.
- Adolescents coinfected with hepatitis B or C virus should be considered for inclusion in coinfection studies of adults.
- Children and adolescents coinfected with tuberculosis or hepatitis B or C virus should be included in clinical trials and pharmacokinetic studies. Innovative strategies to retain coinfected children in ARV drug studies should be incorporated into study designs.
- Regulatory authorities and ethics committees should require and support the inclusion of pregnant women in pre-marketing clinical trials. Women enrolled in Phase II or Phase III clinical trials should not be excluded from the study or taken off the study drug if they become pregnant during the trial unless there are specific reasons to do so.

2.3 Efficient data collection and data sharing

More carefully planning studies of novel ARV drugs for children and more efficiently using existing data can accelerate and streamline the drug development process.

- Pharmacokinetic data for adults can be used in modelling and simulation studies, along with knowledge of physiological changes among infants and other children, to establish starting doses for trials involving children.
- Clinical trials should be carefully designed to maximize efficiency and make best use of resources, by employing innovative designs and statistical methods.
- Early planning and intersectoral communication should ensure that the data generated in clinical trials involving children are fit for purpose; for example:
  - that the weight bands used for dosing within the trial are in accordance with WHO ARV drug dosing recommendations for children; and
  - that the results generated are sufficient for regulatory approval to be granted.
- Washout data obtained from neonates exposed to ARV drugs in utero should be used to support the design of neonatal trials.
- Acceptability data should be collected systematically as part of clinical trials involving children. If data on acceptability of formulations are already available, regulatory authorities should routinely make them available.
- Pooling of data, potentially through large paediatric HIV networks, can maximize the use of existing data on subpopulations such as coinfected children.

- Pharmacovigilance data on pregnant women receiving novel drugs and their exposed infants should be routinely collected, and pharmacovigilance systems in low- and middle-income countries should be expanded.

2.4 Intersectoral communication and coordination

In the past few years, the need for intersectoral collaboration to facilitate the process of developing ARV drugs for children, including supply and logistics, has become increasingly apparent. Several initiatives have emerged, linking drug manufacturers, research networks, regulatory agencies, funding bodies and policy-makers *(1)*. This toolkit highlights approaches for further improving intersectoral communication at various stages of the drug development process, including the following.

- In designing clinical trials, all potential stakeholders should be involved at an early stage, to ensure that trials are aligned as closely as possible with the objectives of funders, regulators and clinicians.
- Drug manufacturers should work closely with clinicians, expert groups and stringent regulatory authorities to ensure that collection of key data is feasible and that the data generated are clinically relevant and meet regulatory requirements.
- Close collaboration and improved coordination between disease areas is also critical to ensure that issues relating to the treatment of coinfected children are considered and that data on these subpopulations are collected in a timely way.
- Collaboration is also needed between formulation scientists, the paediatric HIV research community and social scientists to establish consensus around the assessment of acceptability of ARV formulations for children, including standard criteria for measuring acceptability.
- Target product profiles should be used to communicate product characteristics and anticipate potential problems and should be developed with input from manufacturers, suppliers and regulatory agencies.
- Improved harmonization of regulatory requirements and pathways and regulatory interpretation of stability studies across different regulators would positively influence drug development and supply and logistics.
- Both the United States Food and Drug Administration and the European Medicines Agency are already committed to improving communication across stakeholders, and such efforts should be expanded.
- Donors, funders, country programmes and implementing partners should continue to work together, for example through the Antiretroviral Procurement Working Group, to anticipate and coordinate the procurement of ARV drugs for children.
- Overall, the approach to drug development needs to be harmonized, with efficient communication between policy-makers, the paediatric HIV research community, the pharmaceutical industry, regulatory agencies and funders.

CONCLUSION

This toolkit contributes to a global programme of work encompassed by the Global Accelerator for Paediatric Formulations to ensure faster, more efficient development of optimized treatment options for infectious diseases such as tuberculosis, viral hepatitis and HIV *(2)*. Although it focuses on HIV, many of principles discussed within this toolkit can be extended to other disease areas with similar delays in obtaining treatment options for children. We therefore call on drug manufacturers, researchers, regulatory agencies, funders and other stakeholders to strengthen intersectoral partnerships and work together to incorporate these recommendations into standard practice.

The recommendations outlined in this toolkit aim to simplify, unify and accelerate research and development of drug formulations for children and, ultimately, to expand access to safe, effective and well tolerated ARV drugs for children living with HIV in low- and middle-income countries. This is an essential step towards ensuring that WHO universal treatment guidelines can be adopted and that the Start Free, Stay Free, AIDS Free targets of ending AIDS among children, adolescents and young women by 2020 can be achieved *(3)*.

REFERENCES

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