Research Gaps

World Health Organization

	PADO3 RESEARCH PRIORITIES
Newborns	**A. Neonatal Prophylaxis** •PMTCT risk on maternal DTG – Transmission risk and risk of transmission of DR virus •PMTCT in low risk infants: No ART vs Standard of care •Duration of infant prophylaxis in unsupressed BF mother •AZT prophylaxis dose older than 6 week **B. Newborn Treatment:** •Long acting agents in neonates – PK and safety, muscle bulk issues •Monoclonal antibodies – long acting formulations, •Novel delivery systems •ABC down to <3M •Safety in HIV exposed uninfected **C. Remission research:** IMPAACT P1115, EPIICAL (novel agents, vaccines
Sequencing	**A. Dosing and formulations** -TB-HIV trials: nest PK studies in ongoing trials to gather data in children that acquire TB while on studies -Taste masking and Bioequivalence of crushed tablets -LATs -injectables/patches: 1mo vs 2 mo -Collection of more toxicity data (ie. in children < 3 years and bone/renal effect of TAF) **B. Alternative agents** -INSTIs vs bPIs (i.e. DTG vs bPIs) in NNRTI resistance -Future third line : DTG/Ril and DTG/DRV **C. Innovative strategies** -Dual therapy :DTG/3TC , DRV/r/3TC, DRV/r/DTG in a **non-inferiority trial** including naïve and experienced -Weekend off with DTG/EFV (?)
Novel antivirals	- Broadly neutralizing antibodies (VRC01 in phase II in adults; Vedolizumab (anti- a4b7 integrin) in phase I - Adnectins = molecules that target CD4 and gp41 Combinectin (SC): anti-CD4, anti-gp41,fusion inhibitor, HAS - Nano- formulations & role in pediatric HIV

Many questions are still unanswered

PADO3 RESEARCH PRIORITIES
Newborns

A. Neonatal Prophylaxis

- PMTCT risk on maternal DTG – Transmission risk and risk of transmission of DR virus
- PMTCT in low risk infants: No ART vs Standard of care
- Duration of infant prophylaxis in unsuppressed BF mother
- AZT prophylaxis dose older than 6 week

B. Newborn Treatment:

- Long acting agents in neonates – PK and safety, muscle bulk issues
- Monoclonal antibodies – long acting formulations,
- Novel delivery systems
- ABC down to <3M
- Safety in HIV exposed uninfected

C. Remission research:

IMPAACT P1115, EPIICAL (novel agents, vaccines)

PADO3 RESEARCH PRIORITIES
Sequencing

A. Dosing and formulations

- TB-HIV trials: nest PK studies in ongoing trials
- Taste masking and bioequivalence of crushed tablets
- LATs -injectables/patches: 1mo vs 2 mo
- Collection of more toxicity data (ie. in children < 3 years and bone/renal effect of TAF)

B. Alternative agents

- INSTIs vs bPIs (i.e. DTG vs bPIs) in NNRTI resistance
- Future third line : DTG/Ril and DTG/DRV

C. Innovative strategies

- Dual therapy :DTG/3TC , DRV/r/3TC, DRV/r/DTG in a **non-inferiority trial** including naïve and experienced
- Weekend off with DTG/EFV

PADO3 RESEARCH PRIORITIES
Novel anti-virals

- Broadly neutralizing antibodies (VRC01 in phase II in adults; Vedolizumab (anti- a4b7 integrin) in phase I
- Adnectins = molecules that target CD4 and gp41
- Combinectin (SC): anti-CD4, anti-gp41,fusion inhibitor, HAS Nano-formulations & role in pediatric HIV

NEW:

- Need to better define renal toxicity of TDF 300 mg in children 25-30 kg
- PK data for dose reduction of DRVr
- Efficacy of DTG in second line for failures on RAL-based first-line ART
- PK data to support the use of TAF and DRVr in children on TB treatment
- Efficacy and safety of alternative regimens for PNP

Global research agendas

- Paediatric and Adolescent briefs
- In English and French
- Available online:

https://www.iasociety.org/CIPHER

RESEARCH FOR AN AIDS FREE GENERATION:

A GLOBAL RESEARCH AGENDA FOR ADOLESCENTS LIVING WITH HIV

Worldwide, there were an estimated 2.1 million [1.4 million - 2.6 million] adolescents (10-19 years old) living with HIV in 2016, with 150 adolescents dying from AIDS-related causes every day[1]. Between 2000 and 2015, annual AIDS-related deaths declined for all age groups except adolescents, where mortality more than doubled from 18,000 to 41,000[2].

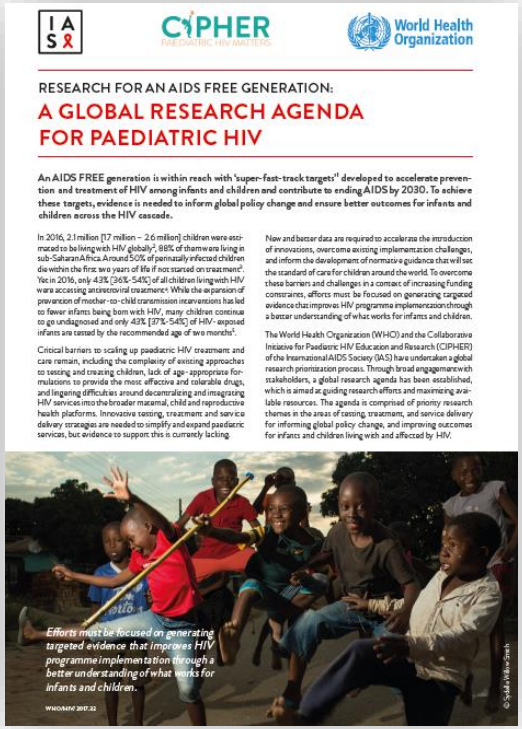
In 2016, there were an estimated 260,000 [150,000-340,000] new HIV infections among adolescents. In sub-Saharan Africa, two out of three newly infected adolescents aged 15-19 years were girls[3]. With the successful scale up and effectiveness of antiretroviral therapy (ART), children living with HIV are surviving and growing into adolescence. This increasing population requires ongoing support to remain in care and adhere to ART, as well as to manage the changes related to adolescence.

Adolescents living with HIV are in urgent need of improved approaches to address their specific health needs. Evidence indicates higher rates of loss to follow up[4], and poor adherence[5], as well as increased needs for psychosocial support[3]. This population group continues to be underserved by current HIV services and have significantly worse access to and coverage of ART[6]. Despite a rapidly growing area of HIV research, a considerable amount of effort is still needed to inform the understanding of what works for this population. Improving outcomes for adolescents and reaching global targets for an AIDS FREE generation by 2030[7] will require evidence-based interventions and policies. These should take into consideration the developmental stage of adolescence while comprehensively addressing the multiple needs of adolescents living with HIV and actively engaging them in their own healthcare. To overcome these barriers and challenges in a context of increasing funding constraints, targeted research is urgently required to bridge identified research gaps and inform policy on adolescent HIV.

The World Health Organization (WHO) and the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) of the International AIDS Society (IAS) have undertaken a global research prioritization process. Through broad engagement with stakeholders, a global research agenda has been established, which is aimed at guiding work and maximizing available resources. The agenda is comprised of priority research themes in the areas of testing, treatment and service delivery for informing global policy change, and improving outcomes for adolescents living with HIV.

Targeted research is urgently required to bridge identified research gaps and inform policy on adolescent HIV.

WHO/HIV/2017.33



RESEARCH FOR AN AIDS FREE GENERATION:

A GLOBAL RESEARCH AGENDA FOR PAEDIATRIC HIV

An AIDS FREE generation is within reach with 'super-fast-track targets'[1] developed to accelerate prevention and treatment of HIV among infants and children and contribute to ending AIDS by 2030. To achieve these targets, evidence is needed to inform global policy change and ensure better outcomes for infants and children across the HIV cascade.

In 2016, 2.1 million [1.7 million – 2.6 million] children were estimated to be living with HIV globally[2], 88% of them were living in sub-Saharan Africa. Around 50% of perinatally infected children die within the first two years of life if not started on treatment[3]. Yet in 2016, only 43% [36%-54%] of all children living with HIV were accessing antiretroviral treatment[4]. While the expansion of prevention of mother-to-child transmission interventions has led to fewer infants being born with HIV, many children continue to go undiagnosed and only 43% [37%-54%] of HIV-exposed infants are tested by the recommended age of two months[5].

Critical barriers to scaling up paediatric HIV treatment and care remain, including the complexity of existing approaches to testing and treating children, lack of age-appropriate formulations to provide the most effective and tolerable drugs, and lingering difficulties around decentralizing and integrating HIV services into the broader maternal, child and reproductive health platforms. Innovative testing, treatment and service delivery strategies are needed to simplify and expand paediatric services, but evidence to support this is currently lacking.

Now and better data are required to accelerate the introduction of innovations, overcome existing implementation challenges, and inform the development of normative guidance that will set the standard of care for children around the world. To overcome these barriers and challenges in a context of increasing funding constraints, efforts must be focused on generating targeted evidence that improves HIV programme implementation through a better understanding of what works for infants and children.

The World Health Organization (WHO) and the Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) of the International AIDS Society (IAS) have undertaken a global research prioritization process. Through broad engagement with stakeholders, a global research agenda has been established, which is aimed at guiding research efforts and maximizing available resources. The agenda is comprised of priority research themes in the areas of testing, treatment, and service delivery for informing global policy change, and improving outcomes for infants and children living with and affected by HIV.

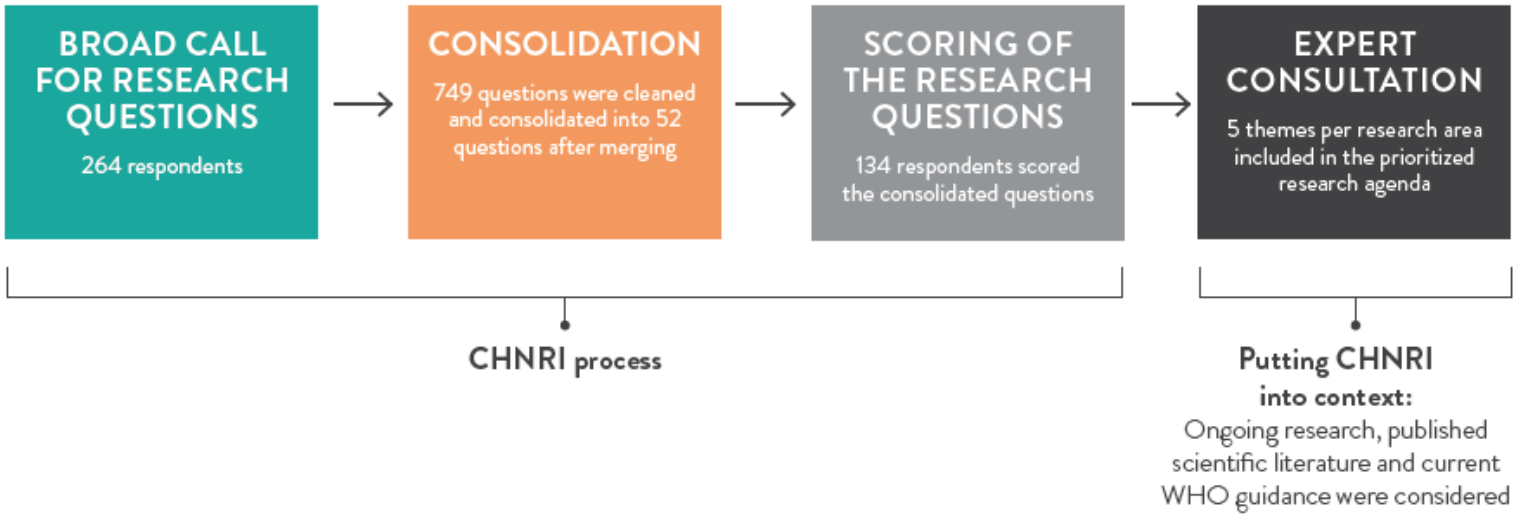
Efforts must be focused on generating targeted evidence that improves HIV programme implementation through a better understanding of what works for infants and children.

WHO/HIV/2017.32

World Health Organization

Methods

- Child Health and Nutrition Research Initiative (CHNRI, www.chnri.org) systematic method for setting priorities in health research



World Health Organization

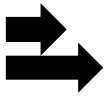
Top 5: Treatment

Children

Safety, efficacy, acceptability, pharmacokinetics and optimal dosing of **existing and new antiretroviral drugs and formulations**, particularly with novel drug delivery systems

Strategies or interventions to improve **adherence** and factors that affect success

Optimal prevention and clinical management of **co-infections**, particularly tuberculosis



Impact of HIV infection and ART on **short- and long-term outcomes**, in particular non-communicable disease

Short- and long-term virologic and immunologic outcomes of **starting very early treatment** in infants living with HIV (impact on functional cure)

World Health Organization

Top 5: Treatment

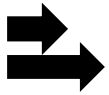
Adolescents

Effective monitoring approaches and strategies to improve **adherence** among adolescents and factors that impact success

Safety, efficacy and acceptability of **novel drug delivery systems**

Prevention and clinical management of **co-infections**, particularly tuberculosis

Optimal **sequencing of ART** in adolescents



Impact of HIV infection and ART on **short- and long-term outcomes** in particular non-communicable diseases

World Health Organization