# Industry Perspectives on HIV Remission/Cure Research in Pediatric Populations

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# Acknowledgements

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# Disclaimer

The questions and comments highlighted during the course of the presentation and discussion are intended to be general in nature and do not reflect a specific strategy by ViiV Healthcare, Merck, or Johnson & Johnson.

# Two Overarching Objectives for Pediatric HIV

- Optimal treatment with age-/weight-appropriate formulations and fixed dose combinations (FDCs) for infants, children, and adolescents

- Support for their families, care-givers, and communities where they reside that are affected by HIV

*These also apply to bringing forward treatments/treatment strategies for HIV remission and ultimately cure in the pediatric space.*

# People Living with HIV...

**People Living with HIV**
(PLWHIV)

**>36,700,000**

Women, Men, and Children

**~2.1 Million Children (<15 years of age)**

***~4-6% of all PLHIV***

*WHO HIV Department, Dec 2016; http://www.who.int/hiv/data/epi_core_2016.png?ua=1*

# People Living with HIV…

| PLWHIV | PLWHIV On Treatment (PLTHIV) |
| --- | --- |
| >36,700,000 | 90:90:90 Goal |
| Women, Men, and Children | Women, Men, and Children |

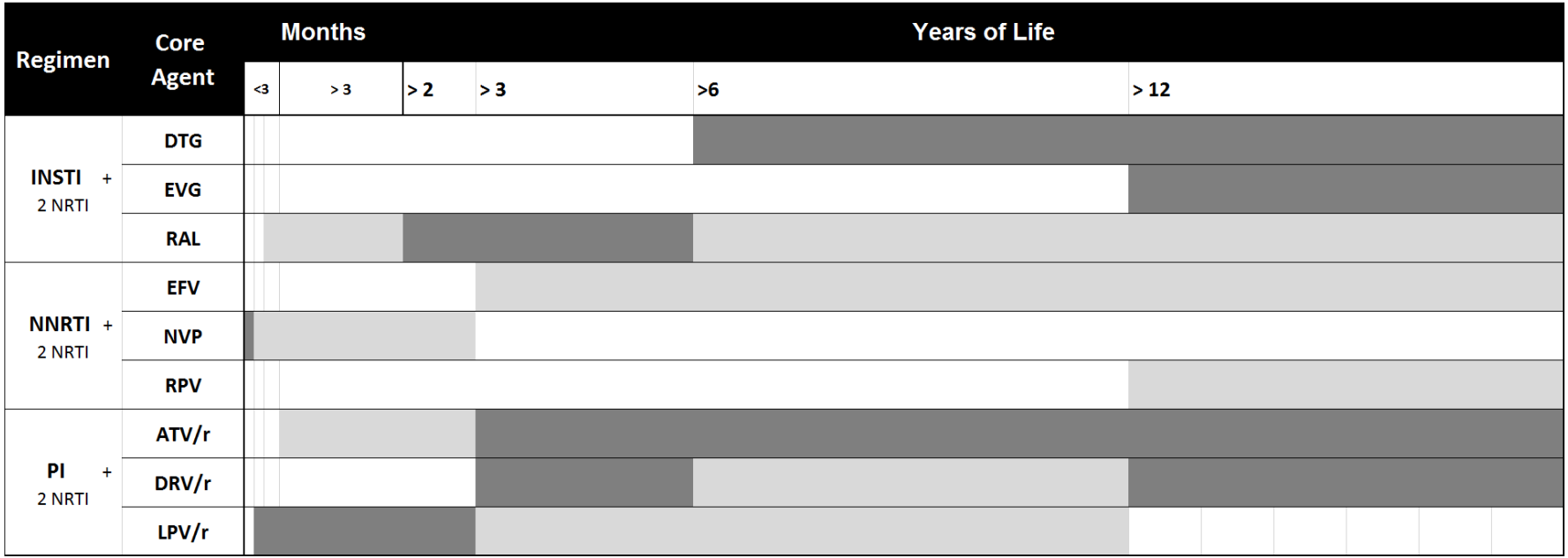
**Increased efforts and resources to provide needed access**

***WHO 2016 Estimates 69% of PLHIV on Treatment****

- ***43% for Children LHIV*****

*http://www.unaids.org/en/resources/documents/2014/90-90-90;*
** http://www.who.int/hiv/data/cascade_global_2016.png?ua=1;*
*** UNICEF, UNAIDS, WHO Global AIDS Monitoring Data, 2017.*

# Preferred and Alternative Regimens by Age and Drug Class*




*alternative* *preferred*

* Adapted from "Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection" http://aidsinfo.nih.gov ; additional details in speaker notes

# People Living with HIV…

| PLWHIV | PLTHIV | PLWHIV in 'remission' (PLRHIV) |
|---|---|---|
| >36,700,000 | 90:90:90 Goal | ? |
| Women, Men, and Children | Women, Men, and Children | People Living with HIV Remission |

**Pediatric examples:**

- **"Mississippi Baby" [3]**
- ***French adolescent* [4]**
- ***CHER Trial child* [5]**

**<1% as "Elite Controllers"[1]**

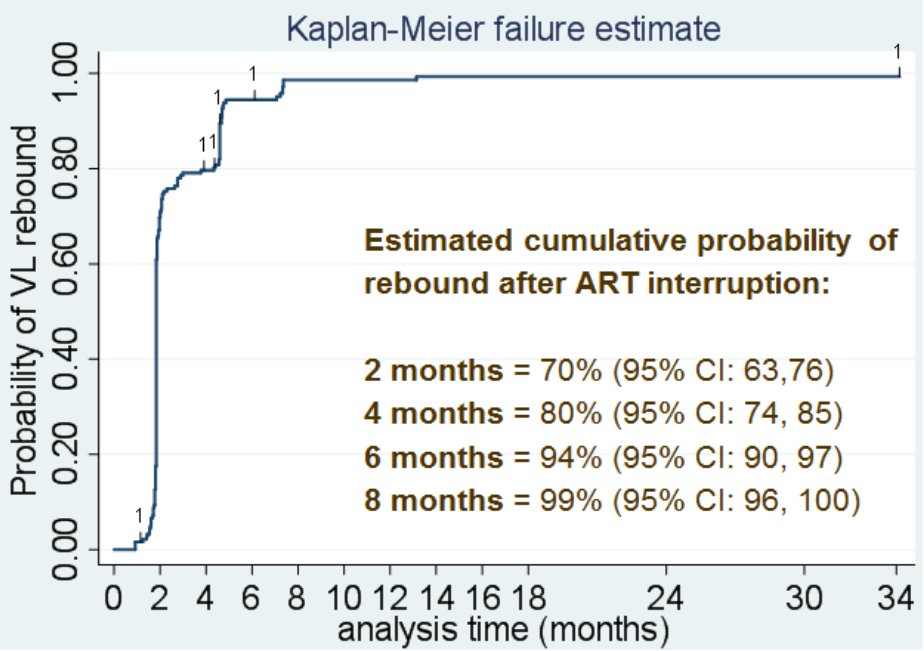
**?% as "Post-Treatment Controllers" [2]**

*[1] Olson et al., PLoS ONE 2014; [2] Saez-Cirion et al., PLoS Pathogens 2013; [3]Persaud et al., NEJM 2013;*
*[4]Saez-Cirion et al., IAS2015, Vancouver, #MOAA0105LB; [5]Violari et al. IAS2017 Paris, #TUPDB0106LB*

# Virologic Rebound Post-Treatment Interruption:

*CHER Trial*

- 70% probability of rebound by 2 months, 99% by 8 months
- 1 Child maintained virologic suppression after more than 8 years off ART




Numbers on the KM curve indicate the times where censoring occurred

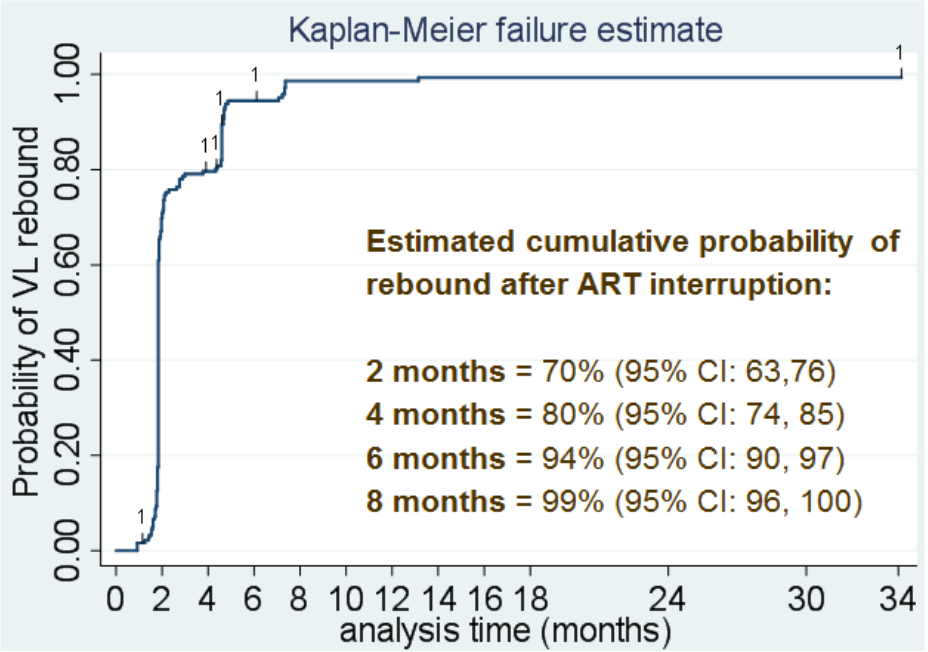
*Adapted from Violari et al., CROI2018 Boston, #137 and Violari et al. IAS2017 Paris, #TUPDB0106LB*

# Virologic Rebound Post-Treatment Interruption:

## *CHER Trial*

- 70% probability of rebound by 2 months, 99% by 8 months
- 1 Child maintained virologic suppression after more than 8 years off ART

***What duration of sustained virologic suppression do we need to achieve with a curative agent/regimen?***

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*Adapted from Violari et al., CROI2018 Boston, #137 and Violari et al. IAS2017 Paris, #TUPDB0106LB*

# People Living with HIV…

| PLWHIV | PLTHIV | PLRHIV | People Living Cured of HIV (PLCHIV) |
|---|---|---|---|
| >36,700,000 | 90:90:90 Goal | ? | 1 |
| Women, Men, and Children | Women, Men, and Children | People Living with HIV Remission | "the Berlin Patient"* |

**10 yr anniversary in Feb 2017!**

*Hutter et al., NEJM 2009; 360:692-698.

# HIV Remission and Cure

| Goal | Clinical Phenotype | Other terms |
|---|---|---|
| **Cure** | • HIV negative*<br>• No need for ARVs<br>• No disease progression | • Eradication<br>• Sterilizing Cure |
| **Remission** | • HIV positive*<br>• Absence of viral rebound off ARVs for an extended period of time<br>• No or delayed disease progression | • Functional Cure |

- We all aspire to achieve HIV Cure, and will continue until we do.
- HIV Remission may be more attainable in the near term.
- Remission/Cure will (likely) be a multi-step, combination approach.

**HIV reservoir in blood and/or tissue; HIV DNA, RNA, Proteins*

**How should/do we approach trying to achieve HIV remission and ultimately cure for the >36,700,000 PLHIV?**

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- Safe
- Simple to administer
- Scalable

*Chun, Moir and Fauci, Nature Immunology 2015*

# How should/do we approach trying to achieve HIV remission and ultimately cure for the >2,100,000 Children LHIV?

***These same factors also apply to pediatrics…..***

- Safe
- Simple to administer
- Scalable

*Chun, Moir and Fauci, Nature Immunology 2015*

# What knowledge/experience applies from developing ARVs for pediatrics?

# Experience From Development of Pediatric ARVs

| Area | Experience | Challenges |
|---|---|---|
| **Study Design/Conduct** | Plasma HIV RNA suppression | Enrolment time and/or study population |
| **Dose/Dose Frequency** | Agent Specific | Weight bands<br>Age |
| **Formulation(s)** | Agent Specific | User friendly |
| **Regulatory** | Submit Pediatric Plans* by the time of Phase 3 Studies for Adults | Potential for different opinions/requirements Western regulators for end users in Africa/Asia |

* *Pediatric Study Plan (PSP) for FDA and Pediatric Investigation Plan (PIP) for EMA*

# Clinical Development Programs for Pediatric ARVs

- Generally well defined and relies upon an accepted surrogate marker for Registration
  - plasma viral load suppression in a relatively short time period such as 24 or 48 weeks

# The Roadmap to HIV Remission/Cure

# How do we find our way?

- Which reservoir(s) and by what measure?
- What clinical endpoint(s) for Registration?

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- Which reservoir(s) and by what measure?
- What clinical endpoint(s) for Registration?

***For adults, adolescents, children, and neonates!***

# Key point

- Clinical development programs for pediatric ARVs is generally well defined and relies upon an accepted surrogate marker for Registration
  - plasma viral load suppression in a relatively short time period such as 24 or 48 weeks
- **Plasma viral load suppression and associated trial designs do not apply to developing agents/regimens for remission and ultimately cure**

## Are there “remission/cure” knowledge gaps that impact development of a curative agent/regimen for pediatric HIV infection?

- Are all approaches evaluated in adults appropriate?
- Is the safety profile required different from adults?
- Are viral reservoirs the same?
- Is Immune context the same?

# Unique Immunity in Infants: Favorable to Achieving HIV Remission

Known timing of infection

Immediate testing and ART

- Limited reservoir and viral diversity
- Preserved immunity
- Excellent response to vaccines

Typical pediatric immune response compared to an adult:

**Higher:**

- Naïve CD4
- Treg
- CXCL8+CD8

**Lower:**

- Cytokines
- B cell
- Th1
- IFNY+CD8

*Takata, Blood 2012; Gibbons, Nature Med 2014; Ananworanich, AIDS 2014; Uprety, CID 2015; van Zyl, JID 2015*
*Martinez-Bonet CID 2015; Wang, Leuk Biol 2015; Klein, Lancet ID 2015; Palma, BMC ID 2016*

*Slide Courtesy Dr Jintanat Ananworanich, US MHRP*

**In the absence of a clinically validated surrogate marker as a Regulatory accepted endpoint for "remission" or "cure", how do we determine clinical relevance?**

- Analytical treatment interruption (ATI)?
- How to design ATI? Who to allow?
- How long is relevant for Regulatory file?

# Questions