## IMPAACT P1115 Study

Phase I/II proof of concept study to assess HIV remission among neonates with *in utero* HIV infection who initiate early intensive therapy within 48 hours of birth. Remission: No confirmed plasma HIV-1 RNA greater than or equal to the limit of detection of the clinical assay through 48 weeks of ART cessation.

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
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<tbody>
<tr>
<td>Step 1</td>
<td>Initiation of intensive ART for high-risk infants while awaiting HIV test results (switch to standard prophylaxis if infection is not confirmed)</td>
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<tr>
<td>Step 2</td>
<td>Continued intensive ART for confirmed HIV-infected infants with monitoring to determine eligibility for cessation of ART between 2 and 4 years of age</td>
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<tr>
<td>Step 3</td>
<td>ART cessation with monitoring for viral rebound through 5 years from the date of entry into Step 3</td>
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<tr>
<td>Step 4</td>
<td>ART re-initiation for infants who experience viral rebound after ART cessation through 5 years of age or until 6 months after re-suppression on ART (whichever is later)</td>
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</tbody>
</table>
Guiding Questions

Expert panel recommendations

Who is eligible for ART cessation

What is ultimate judgment of acceptable risk benefit ratio (prospect of direct benefit or no more than minor increase over minimal risk)

How many failures will change that assessment

Should ART cessation be considered for any study participant in version 1.0 of P1115

How many participants should experience viral rebound before further ART cessation is not recommended

How to modify the approach?
Risk/Benefit Considerations

ONLY WAY TO DETECT REMISSION
MINIMAL RISK OF RESISTANCE
RESUPPRESSION NOT A PROBLEM
NO CONCERNS ABOUT IMMUNE RESTORATION
MINIMAL CONCERN ABOUT RESERVOIR SEEDING
CONCERN FOR CNS SEEDING
SIGNAL THAT CAN BE STRENGTHENED
EQUIPOISE AND ETHICAL
Risks of Rx interruption:
acute retroviral syndrome
disease progression (only if not monitored carefully; not a risk if re-suppress quickly)
misinterpretation of experimental nature of treatment cessation that it is acceptable/recommended to take treatment holidays
selection of ARV resistance mutations (unlikely)
Frequent blood draws required to monitor VL while off Rx

Benefits of Rx interruption:
only way to identify possible remission
auto-immunize against own viral strain if virus rebounds
reduced drug-related toxicity
reduced drug cost
psychological benefit of not having to take drugs
Cohorts 1 and 2: 54 entered Step 2

Cohort 1: 440 enrolled in Step 1
Cohort 1: 34 entered Step 2
Cohort 2: 20 enrolled in Step 2

Cohorts 1 and 2: 54 entered Step 2
31 currently on-study in Step 2

Under Version 1.0:

Under Version 2.0, 445 mother-infant pairs are expected to be enrolled within a period of three years.
Step 3 Entry Criteria

*Updated with expert panel recommendations*

General Criteria:

Permanent cessation of breastfeeding and no exposure for at least 6 weeks prior to screening.

High likelihood of continued participation and adherence in the study in accordance with the protocol

Separate informed consent for entry into Step 3
Step 3 Entry Criteria

Informed consent:

Develop tools to facilitate and monitor understanding of consent forms.

Recommend extended time for understanding an information sheet.

An open ended discussion involving a feedback approach.

Encourage mother to involve other members of the family in the informed consent as appropriate.

Community involvement in the development of the informed consent.

Early engagement of local IRB’s (including hospital regulatory bodies).

Consider workshops to explain the study concept.
Step 3 Entry Criteria

*Updated with expert panel recommendations*

**Virologic criteria**

No target detected on all plasma HIV RNA at Step 2 Week 48 and thereafter

No detectable HIV DNA on two consecutive HIV DNA tests at least 8 weeks apart and with at least 850,000 PBMCs assayed

An HIV RNA test at the time of second DNA test should be undetectable with target not detected
Step 3 Entry Criteria

*Updated with expert panel recommendations*

**Immunologic criteria:** The two consecutive negative HIV antibody tests should be by fourth generation ELISA rather than Western blot.

CD4 cell percentage ≥ 25% and absolute CD4 cell count above lower limit of normal range for age.
Step 3 Entry Criteria

Monitoring Viral Rebound:
Weekly monitoring for 8 weeks followed by every 4 weeks for the duration of time off ART
Use of point of care assays; prompt confirmation of positives; with result obtained within 72 hours of the point of care assay
Restart ART for any results above the limit of quantification of the assay

The majority of the committee agreed with the current study monitoring guideline to trigger a Study Monitoring Committee (SMC) review if 10/10 children who interrupt ART experience rebound within 48 weeks. A minority view was expressed that an SMC review should be triggered if 8/8 children who interrupt ART experience rebound within 48 weeks.
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