Second and third line paediatric ART strategies

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Second and Third Line ART Strategies among Children and Adolescents

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# Disclosures

<table>
<thead>
<tr>
<th>Research Support/P.I.</th>
<th>NIH, PEPFAR</th>
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<tr>
<td>Employee</td>
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<td>Scientific Advisory Board</td>
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Presentation includes discussion of the off-label use of a drug or drugs
Introduction

- With expanded global access → Increasing numbers of children and adolescents are failing first-line ART in low- and middle-income countries.
- To ensure that perinatally HIV-infected children survive into adulthood need for:
  - Better access to viral load monitoring
  - 2\textsuperscript{nd}- and 3\textsuperscript{rd}-line ART options
  - Research to guide optimal regimen selection
- ART Rx failure occurs early in childhood, as well in adolescence.
- Studies of salvage drug options have been primarily conducted in adults
- Urgent Need for:
  - Evidence-based approaches to paediatric and adolescent regimen selection
  - Paediatric drug formulations and
  - Expanded access to novel drugs
### 3 Types of Failure

<table>
<thead>
<tr>
<th>Virological</th>
<th>Immunological*</th>
<th>Clinical*</th>
</tr>
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<tbody>
<tr>
<td>Viral load is never fully suppressed to &lt;1000 copies/ml by 6 months after initiation of HAART</td>
<td>CD4 persistently falls below the baseline CD4</td>
<td>Recurrence or persistence of AIDS-defining conditions</td>
</tr>
<tr>
<td>After initial suppression 2 detectable viral loads within a 3 month period</td>
<td>CD4 fails to increase by more than 25-50 cells/μL after 1 year of treatment</td>
<td>Persistent decline in weight/height despite adequate nutrition or other explanation</td>
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<td>&gt; 50% decline in CD4 from its highest level on HAART</td>
<td>Developmental failure</td>
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*Immunologic or clinical failure in the presence of full virologic suppression may or may not justify a change in HAART*
Switching to Second Line

- If VL > 1000 copies/ML on 2 consecutive measurements within 3 – 6 months with adherence support, diagnose treatment failure and switch to 2nd line
- If VL measurement is not available, clinical and immunological criteria for failure can be used
- Principle: Never switch 1 drug, unless in cases of intolerance or toxicity
## Recommended 2nd Line Regimens in Children and Adolescents

<table>
<thead>
<tr>
<th>Second-line ART</th>
<th>Preferred regimens</th>
<th>Alternative regimens</th>
</tr>
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<tbody>
<tr>
<td>Adults and adolescents (≥10 years), including pregnant and breastfeeding women</td>
<td>AZT + 3TC + LPV/r&lt;sup&gt;a&lt;/sup&gt; AZT + 3TC + ATV/r&lt;sup&gt;a&lt;/sup&gt;</td>
<td>TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r</td>
</tr>
<tr>
<td>If a NNRTI-based first-line regimen was used</td>
<td>ABC + 3TC + LPV/r&lt;sup&gt;b&lt;/sup&gt;</td>
<td>ABC + 3TC + LPV/r&lt;sup&gt;b&lt;/sup&gt; TDF + 3TC (or FTC) + LPV/r&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If a PI-based first-line regimen was used</td>
<td>No change from first-line regimen in use&lt;sup&gt;c&lt;/sup&gt;</td>
<td>AZT (or ABC) + 3TC + NVP</td>
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<tr>
<td>&lt;3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 years to less than 10 years</td>
<td>AZT (or ABC) + 3TC + EFV</td>
<td>ABC (or TDF) + 3TC + NVP</td>
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</table>

<sup>a</sup>DRV/r can be used as an alternative PI and SQV/r in special situations; neither is currently available as a heat-stable fixed-dose combination, but a DRV + RTV heat-stable fixed-dose combination is currently in development.

<sup>b</sup>ATV/r can be used as an alternative to LPV/r for children older than six years.

<sup>c</sup>Unless failure is caused by lack of adherence resulting from poor palatability of LPV/r.

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3rd Line Regimens
Children and Adolescents

- No standardized, “recommended” 3rd line regimen
- Best guided by genotypic resistance assay
- Consult an HIV Specialist
- Patients who are failing a boosted PI regimen are very unlikely to have resistance
  - Poor adherence is the likely culprit
  - If they previously received an unboosted PI, resistance is possible (i.e., nelfinavir, saquinavir, ritonavir)
3\textsuperscript{rd} Line Regimens

Paediatrics and Adolescents

Requires very close and intensive management

- Refer to specialist HIV management centre
- Intensive psychosocial and adherence evaluation
- Intensive follow-up
  - Frequent clinic visits
  - Home visits
- Search for causes of failure
  - Medical
  - Social
  - Adherence
- Give indicated prophylaxis: cotrimoxazole

\textit{NB: Please note these measures are helpful even for 1\textsuperscript{st} line failure}
3rd Line Regimens
Paediatrics or Adolescents

Genotypic Resistance Assays

- Send while patient is:
  - Still taking the failing 2nd line regimen (preferred) OR
  - Within 4 weeks of discontinuation of the failing regimen
- Do not wait for more than 4 weeks for resistance assay to return
- If does not return in 4 weeks, discuss with an HIV Specialist for recommendations for prompt switching to an empiric 3rd line regimen, pending eventual return of the resistance assay
3rd Line Drug Options

- Darunavir/ritonavir (DRV/r)
- Atazanavir/ritonavir (ATV/r)
- Lopinavir/ritonavir (LPV/r)
- Raltegravir (RAL)
- Etravirine (ETR)
  - Plus an optimized background regimen

NB: Regimen best guided by genotypic resistance assay results
ARIEL: Objectives and study design

- Primary objective: To assess the PK and short-term safety/efficacy of darunavir/r with ≥2 active NRTIs to support dose recommendations by bodyweight in treatment-experienced children 3–<6 years over 24 weeks.

  - Treatment-experienced children aged 3 to <6 years
  - Weight 10 to <20kg
  - HIV-1 RNA >1000 copies/mL
  - <3 darunavir RAMs¹ at screening
  - On HAART for ≥12 weeks

Darunavir/r + OBR* (N=27)

*Investigator-selected OBR consisted of ≥2 active NRTIs

Primary analysis at Week 24

Follow-up to Week 48

Initial dose as darunavir oral suspension (100mg/mL) 20mg/kg bid plus RTV 2.6–3.2mg/kg bid; After predefined Week 2 PK analysis and DSMB recommendations, darunavir/r dose amended to 25mg/kg bid for patients weighing <15kg (plus 2.6–3.2mg/kg bid RTV) and 375mg bid fixed (tablet formulation) for patients weighing 15–<20kg (plus 50mg bid RTV).

¹DRV RAMs include the following mutations: V11I, V32I, L33F, I47V, I50V, I54L, I54M, T74P, L76V, I84V and L89V

Violari A, et al, 18th CROI 2011; abstract 713
CD4+ cell percentage increased from baseline to Week 24 (ITT-NC=F) by mean 3.8%

Violari A, et al, 18th CROI 2011; abstract 713
ARIEL: Conclusions

- Over 24 weeks of treatment, darunavir/r and an OBR was effective and generally well tolerated in HIV-1-infected, treatment-experienced pediatric patients aged 3 to <6 years.

- At Week 24:
  - 56% of patients had HIV-1 RNA <50 copies/mL (ITT-TLOVR)
  - No new safety concerns were reported and most AEs and laboratory abnormalities were grade 1 or 2 in severity.
  - No development of resistance was observed in virologic failures.

- These findings support the use of darunavir/r and an OBR in treatment-experienced, HIV-1-infected patients aged 3–<6 years at the following doses:
  - Darunavir/r 25/3mg/kg bid for patients weighing 10–<15kg.
  - Darunavir/r 375/50mg bid for patients weighing 15–<20kg.

Violari A, et al, 18th CROI 2011; abstract 713
DELPHI Part II: Study design

- Phase II, open-label trial
  - 6–17 years old
  - HAART ≥12 weeks
  - HIV RNA ≥1000 copies/mL
  - N=80 (44 from Part I plus 36 additional children)

**48 weeks**

- Darunavir 11–19mg/kg + RTV 1.5–2.5mg/kg bid + OBR: ≥2 ARVs

Patients received darunavir as 75mg and 300mg tablets:

- 20–<30kg: darunavir/r 375/50mg bid (n=20)
- 30–<40kg: darunavir/r 450/60mg bid (n=24)
- ≥40kg: darunavir/r 600/100mg bid (n=36)

- All patients received an OBR of ≥2 ARVs; NRTIs: lamivudine (47.5%), tenofovir (45.0%), zidovudine (40.0%), didanosine (30.0%); NNRTIs: efavirenz (5%), nevirapine (1.3%); Enfuvirtide (30%)

CD4+ cell count increased from baseline to Week 48 (ITT-NC=F) by mean 147 cells/mm³
DELPHI Part II: Conclusions

- In treatment-experienced, HIV-1-infected children and adolescents aged 6–17 years, darunavir/r showed
  - Comparable exposure to adults with appropriate dose selection
  - Good virologic response rates in the presence of <3 darunavir RAMs
- No statistically significant changes in total cholesterol/HDL ratio or mean glucose were seen
- At the recommended pediatric dose, darunavir/r can be effective in patients with <3 darunavir RAMs and has a neutral lipid and glucose safety profile

IMPAAACT P1066 Design

- Multicenter, Open Label, Non-comparative Study of RAL in 2 Stages:
  - Stage 1- Dose Finding & Chronic Therapy Extension (intensive PK)
    - AUC: 14 µM/hr; C12h: 30nM
  - Stage 2- Chronic Therapy at Selected Dose
- Total N= ~140
- Eligibility:
  - VL > 1000 and failed* at least one ART regimen, ages 2-18 yrs
  - Age strata enrolled sequentially, oldest first
    - Cohort I (12 - 18 yrs)
    - Cohort II (6 - 11 yrs)
    - Cohort III (2 - 5 yrs)
    - Cohort IV * (6 mos - 2yrs)
    - Cohort V * (4wks - 6 mos)
  - *Failure/treatment experience may be HIV infection occurring despite PMTCT (direct treatment not required)

Nachman et al. AIDS 2012 Washington D.C.
Endpoints:
- Safety: Grade 3+ or serious adverse events (AE)
- Efficacy:
  - Primary: vRNA < 400c/mL or ≥1 log reduction
  - Secondary: vRNA < 50c/mL, change in CD4 count (%)
  - Used Observed Failure missing data approach
- Time points:
  - Primary: 24 wk
  - Secondary: 48 wk

Analysis Populations:
- Primary: subjects who received only the final selected dose
- ITT population: all treated subjects

Here we present demographics and 48 week safety and efficacy data in 96 subjects 2-18yr (Cohorts I-III) who received RAL only at the final selected dose
Efficacy: Percent of Patients (95% CI) with vRNA<400 c/mL or 1 \text{Log}_{10} \text{ Decline from Baseline (Final Dose)}
Two RAL formulations were studied in HIV infected youth ages 2 to 18 years; PK targets were met for both formulations.

At the selected final doses RAL was well-tolerated and showed favorable virologic and immunologic responses through 48 weeks of treatment.

Data from All Treated subjects (who received other than final dose, N=126) were consistent.
Early Outcomes of Darunavir- and/or Raltegravir-based Antiretroviral Therapy in Children with Multidrug-Resistant HIV at a Paediatric Center in Botswana

- Retrospective chart review of 4 multi-drug resistant paediatric patients on DRV/r- and/or RAL-based regimens.
- Viral load, CD4 count, adherence by pill count, and WHO clinical stage prior to and after switch to DRV/r- and/or RAL-based regimen, ART, genotypic resistance assays reviewed for mutations present prior to switch.

Results:
- All patients achieved viral suppression,
- All showed improved/stable CD4 counts, and
- All obtained or maintained WHO clinical treatment stage I, even after long-standing virologic/immunologic failure.

Conclusion:
- DRV/r- and/or RAL – based 3rd line regimen were well tolerated and effective in children and adolescents in resource-limited settings failing ART due to ritonavir-boosted lopinavir (LPV/r) resistance.

Kirk et al. JAPAC 2013
Treatment Monitoring

- To assure success of therapy
  - Clinical improvement
  - Immunologic recovery
  - Virologic suppression
  - Sustained good adherence and prevention of resistance

- To detect complications of therapy
  - Intolerance
  - Toxicity
Clinical Monitoring

- Possible ARV side effects/intolerance
- New symptoms
- Growth/development
- Adherence
- Disclosure
- Clinical screening for TB or TB exposures
- Preventative health
  - Prevention counselling
  - Nutrition
  - Smoking avoidance
  - Avoidance of ingested traditional medicines
Adherence

- Adherence assessment includes:
  - Subjective assessment
    - Asking the patient and/or caregiver about adherence
    - Reviewing doses and timing, side effects/intolerance, other medications being utilized (e.g., traditional meds)
  - Objective assessment
    - Pill count
    - Liquid medication measurement or estimation
  - Positive reinforcement of excellent adherence
  - Plan and close follow-up of poor adherence
Summary

- Treatment success = improvement in clinical condition, VL <1000 copies/ml, increase in CD4 cell count
- Three types of treatment failure:
  - Virologic
  - Clinical
  - Immunologic
- Viral Load is the most sensitive marker of treatment failure
- ARV drug resistance is an important cause of treatment failure, but other causes must also be considered and ruled out
- Do not keep a patient on a failing regimen for a prolonged period of time
Emerging Challenges

- Growing number of adolescents with complex psychosocial issues
- Designing programs to ensure smooth transition of HIV-infected adolescents into adulthood
- Sustainability of National ARV Programs - Donor Fatigue
- Management of side-effects related to chronic exposure to ARVs
- Need for Evidence-based approaches to paediatric and adolescent regimen selection, paediatric drug formulations and expanded access to novel drugs