Paediatric Transition

Dr. Edmund Wilkins
Head of the HIV Clinical Trials Unit
North Manchester General Hospital
“Support needing populations through medical assistance and the transfer of knowledge to local medical practitioners.”

Our vision for the Medical Assistance & Medical Education (MAME) Programs
Times have changed

• Prolonged survival now expectation
• Children with vertically acquired HIV infection may well have near normal life expectancy
Plan

• Introduction
  • UK
  • Global

• Presentation

• Treatment and guidelines
  • When to start
  • What to start

• Transition of care
Regional distribution of main follow-up clinic for 1245 children alive and followed up in CHIPS

- London: 697 (56%)
- Scotland: 46 (4%)
- Rest of England: 422 (34%)
- Ireland: 59 (5%)
- Wales: 16 (1%)
- N. Ireland: 5 (0%)

Children who have died, lost to follow-up, left the UK & Ireland or transferred to adult care are excluded.
Age distribution* of children in follow-up by year, 1996-2009
Care slowly transfers

PAEDIATRICIAN  TRANSITIONAL  ADULT
Note: Data are for all children and young people alive who were ever in follow-up from 1996 onwards, including children who have since transferred to adult care; those who subsequently died or were lost to follow-up are excluded from the year of death or loss to follow-up. All paediatric infections are included, regardless of mode of acquisition (94% perinatal). CHIPS includes all diagnosed HIV-infected children known to be living in the UK/Ireland, of whom ~55% were born abroad. Data for 2013 are incomplete as subject to reporting delay.
Global summary of HIV epidemic 2013

| Number of people living with HIV in 2013 | Total   | 35.0 million [33.1 million – 37.2 million] |
|                                         | Adults   | 31.8 million [30.1 million – 33.7 million] |
|                                         | Women    | 16.0 million [15.2 million – 16.9 million] |
|                                         | Children (≤15 years) | 3.2 million [2.9 million – 3.5 million] |

| People newly infected with HIV in 2013 | Total   | 2.1 million [1.9 million – 2.4 million] |
|                                         | Adults   | 1.9 million [1.7 million – 2.1 million] |
|                                         | Children (≤15 years) | 240 000 [210 000 – 280 000] |

| AIDS deaths in 2013 | Total   | 1.5 million [1.4 million – 1.7 million] |
|                     | Adults   | 1.3 million [1.2 million – 1.5 million] |
|                     | Children (≤15 years) | 190 000 [170 000 – 220 000] |
Children receiving ART 2013

## Gauging recent progress in the global HIV response

<table>
<thead>
<tr>
<th>2013</th>
<th>2009-2013</th>
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<tbody>
<tr>
<td>1.5 million HIV related deaths</td>
<td>▼ 25%</td>
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<td>[1.4 – 1.7 million]</td>
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<tr>
<td>320 000 TB-related deaths in PLWHA*</td>
<td>▼ 36%**</td>
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<td>[300 000 – 340 000]</td>
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<tr>
<td>2.1 million HIV infections</td>
<td>▼ 15%</td>
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<tr>
<td>[1.9 – 2.5 million]</td>
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<tr>
<td>240 000 HIV infections in children</td>
<td>▼ 40%</td>
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<tr>
<td>[210 000 – 280 000]</td>
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</table>
Adolescents living with HIV – male/female 2012
The gap between access to ART for children and adults continues to widen

**Adults**
- 9,0 m
- + 21%
- 10,9 m

> 1 in 3 adults with HIV on ART (37%)

**Children**
- 640 k
- + 15%
- 740 k

1 in 4 children with HIV on ART (23%)

Uptake of 2013 WHO guidelines increases eligibility for treatment

Percentage of 58 WHO HIV Focal Countries with confirmed adoption of select WHO 2013 ARV recommendations, June 2014

Source: WHO HIV Country Intelligence Database, June 2014
Incidence and prevalence HIV 2013
SE Asia

**Incidence**
- 20% China
- 23% Indonesia
- 38% India

**Prevalence**
- 43% India
- 17% China
- 13% Indonesia
- 5% Viet Nam
- 9% Thailand
- 4% Myanmar
- 2% Malaysia
- 2% Cambodia
- 1% Nepal
- 1% Pakistan
- 3% Rest of the region

- 0.6% Papua New Guinea
- 0.6% Philippines
- 2% Thailand
- 4% Viet Nam
- 4% Pakistan
- 2% Myanmar
Myanmar: annual cumulative and new HIV cases, 1989-2010

Myanmar: HIV prevalence among young key populations (15-24), 2000-2013

<table>
<thead>
<tr>
<th>Year</th>
<th>FSW</th>
<th>PWID</th>
<th>MSM</th>
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<td>2007</td>
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<td>2013</td>
<td>7.1</td>
<td>11.7</td>
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Differences between Adults and Children

• OI in children often reflects primary infection rather than reactivation
• Different disease manifestations
• OI occurs at a time when infant’s immune system is immature
• Early symptomatic disease is invariably an indication for treatment
• Some conditions much commoner in children than adults
• Classical features of infection may not be present
Difficulty of Diagnosing OI in Children

• Inability to describe symptoms
• Antibody-based tests confounded by maternal transfer of antibody
• Samples often difficult to obtain without invasive procedures
Frequency of OI among HIV-Infected Children *in the pre-ART era*

- Pre-HAART era, most common OIs occurring at >1 events/100 child years
  - Serious bacterial infections (bacteremia and pneumonia), herpes zoster, *Pneumocystis jiroveci* (*carinii*) pneumonia, candidiasis, *Mycobacterium avium* complex
- Pre-HAART era, most common OIs occurring at <1 events/100 child years
  - Cytomegalovirus, toxoplasmosis, cryptosporidiosis, TB, systemic fungal infections
## Changes in Frequency of OI among HIV-Infected Children

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pre-HAART Rate per 100 Child Years</th>
<th>Post-HAART Rate per 100 Child Years</th>
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<tbody>
<tr>
<td>Bacterial pneumonia</td>
<td>11.1</td>
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<td>Herpes zoster</td>
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<td>1.1</td>
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<tr>
<td>Disseminated Mycobacterium avium</td>
<td>1.8</td>
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<tr>
<td>Pneumocystis jiroveci</td>
<td>1.3</td>
<td>0.09</td>
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</table>
Common presentations in children

Images from Dr Wilkins & Dr Siranthana
Common presentations in children

Images from Dr. Wilkins
Presentations in children

• Failure to thrive
• Development delay (especially neurological)
• Fall off on growth centiles
• Delayed puberty
• Recurrent ENT infections
• Severe/unusual viral infections
  • Cutaneous (HPV, Molluscum, HS, HZ)
  • Systemic (RSV, VZV, measles, adenovirus)
• Disseminated BCG
Bacterial pneumonia

• Most common infection in pre-HAART era (15/100 child years)
• Because of difficulties in obtaining appropriate diagnostic specimens, bacterial pneumonia is often a presumptive diagnosis in a child with fever, pulmonary symptoms, and an abnormal CXR

Images from Dr Siranthana
Serious Recurrent Bacterial Infections:

- Bacteria isolated include:
  - *Streptococcus pneumoniae*,
  - *Haemophilus influenzae* type B,
  - *Staphylococcus aureus*,
  - Gram –ve (*E. coli, Pseudomonas, non-typhoid *Salmonella*)
- *S pneumoniae* accounts for >50% of bacteremia
- Increased rate of bacteremia
- Gram-negative bacteremia more common in children with advanced disease
*Pneumocystis jiroveci* (carinii): Epidemiology

- Most common AIDS indicator disease in children
- Incidence highest in first year of life, peaking at 3-6 months
- Accounted for 57% of AIDS-defining illnesses in infants age <1 year pre-ART
- CD4 T-cell count not a good indicator of risk in infants <1 year old
- Infection now unusual owing to routine prophylaxis with TMP-SMX
**Pneumocystis jiroveci (carinii):**

Clinical Manifestations

- Fever, tachypnea, cough, dyspnea, poor feeding, weight loss
- Extra-pulmonary locations: spleen, liver, colon, pancreas, ear, eye, GI tract, bone marrow, heart, kidney, lymph nodes, CNS

Images from Dr Wilkins
Pneumocystis jiroveci (carinii): Prevention

- Chemoprophylaxis with TMP-SMX recommended as follows, based on CD4 counts and patient age:
  - 6 years: CD4 count <200 cells/µL or CD4 percentage <15%
  - 1 to 5 years: CD4 count <500 cells/µL or CD4 percentage <15%
  - All HIV-infected infants <12 months of age regardless of CD4 count or percentage
Lymphocytic interstitial pneumonitis

- 40% of children
- EBV co-factor
- Disease asymptomatic or mild
- CXR shows diffuse reticulo-nodular changes
- Occasionally symptoms:
  - Chronic onset
  - Cough, SOB, low grade fever
- Diagnosis by TBB
- Treatment not indicated

Images from Dr Wilkins
Tuberculosis in HIV

More likely:

• Infection after exposure
  • 10-20% vs 5-10%
• Progressive primary disease after infection
  • 30% vs 5-10%
• Reactivation of latent infection
  • 5-10% annual vs 5-10% lifetime
• Reinfection with new strain
  • 50:50 vs 90:10

• Reduced smear-positive rates in pulmonary TB (40%)
• Less cavitation and atypical chest x-ray appearance with lower CD4 count
• Increased disseminated disease and extra-pulmonary infection with lower CD4
  • > 60% vs <20%
• Greater risk of adverse drug reactions
TB

Images from Dr Wilkins
Features of primary TB

Disease
- Lymphadenopathy
  - Collapse
  - Consolidation
  - Obstructive emphysema
  - Cavitation
- Pleural effusion
- Endobronchial
- Miliary
- Meningitis
- Pericarditis
# MDRTB/XDRTB

![Images from Dr Wilkins](image1.jpg)

<table>
<thead>
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<th></th>
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Images from Dr Wilkins
Other disseminated infections

Images from Dr Wilkins & Dr Siranthana
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Treatment guidelines
Many guidelines still informed by adult trial data
CD4% normal range by Age

ECS PIDJ 1992;11:1021
CD4 count after starting treatment
ART recommendations

• ART is recommended:
  • For all children under 1y of age
  • For all children with significant disease
  • Asymptomatic children >1y based on age-specific CD4 thresholds
  • For all children with hepatitis B/C co-infection

• ART should be considered:
  • In all children aged 1-3y
  • If the VL is >100,000 c/ml
  • If significant HIV-related symptoms
  • In sexually active adolescents as part of TASP
## Comparison of current treatment guidelines

<table>
<thead>
<tr>
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<th>WHO 2013</th>
<th>DHHS 2014</th>
<th>PENTA 2014</th>
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<tr>
<td>&lt;1y</td>
<td>ALL</td>
<td>ALL</td>
<td>ALL</td>
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<tr>
<td>1-3y</td>
<td>ALL</td>
<td>CD4 &lt;1000 &lt;25%</td>
<td>CD4 &lt;1000 &lt;25%</td>
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<td></td>
<td>CDC Category B/C</td>
<td>CDC Category B/C</td>
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<td>VL &gt;1000 c/ml</td>
<td>WHO stage 3/4</td>
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<td>Prioritise:</td>
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<td>Consider: ALL</td>
<td>Consider:</td>
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<td>- 1-2y</td>
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<td>- ALL</td>
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<td>- WHO stage 3/4</td>
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<td>- VL &gt;1000 c/ml</td>
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<td>- CD4 &lt;750 &lt;25%</td>
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## Comparison of current treatment guidelines

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<th>DHHS 2014</th>
<th>PENTA 2014</th>
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<td>3-5y</td>
<td>ALL</td>
<td>CD4 &lt;750 &lt;25%</td>
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<td>&gt;5y</td>
<td>CD4 &lt;500</td>
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<td>- VL &gt;1000 c/ml</td>
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ART regimen

• For naïve children <1y:
  • NVP and LOP/r considered preferred options
    • Exception is for children exposed to NVP as part of failed MTCT
  • 4 drug regimen preferred over 3 (CHIVA)
  • NRTI backbone ABC, 3TC, AZT

• Alterations with age for 3rd drug:
  • NVP as preferred NNRTI for children <3y and EFV for children >3y
  • LOP/r as preferred boosted PI for children aged <6y, ATAZ/r for children >6y, and ATAZ/r or DAR/r for children >12y
  • RAL is as an option for children >12y
# Recommended treatment

## PENTA

<table>
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<tr>
<th></th>
<th>&lt;1y</th>
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<td>ABC/3TC</td>
<td>ABC/3TC</td>
<td>ABC/3TC</td>
<td>ABC/3TC</td>
<td>TDF/FTC ABC/3TC</td>
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<td><strong>3rd agent</strong></td>
<td>LPV/r NVP</td>
<td>LPV/r NVP</td>
<td>LPV/r NVP</td>
<td>ATZ/r EFV</td>
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<td><strong>Alternative 3rd agent</strong></td>
<td>NVP DAR/r LPV/r</td>
<td>NVP LPV/r RAL DTG</td>
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HIV prognosis in children is improving

3,553 children
Median f/u 5.3 yrs
298 deaths

Mean age at death 1994: 8.9 years
Mean age at death 2006: 18.2 years

Age at Death by Year of Death for Infected Children

PACTG 219

Median Age at Death (IQR)
10yrs onwards

- Paediatricians
- Adult physicians

Paediatric
Family clinic
Transitional
Adolescent
Young adult

Vertical transmission

Horizontal transmission
Paediatricians

Adult physicians

Paediatric

Family clinic

Transitional

Adolescent

Young adult

Vertical transmission

Horizontal transmission

10yrs onwards
Of 1245 perinatally infected children in CHIPS (2010)

- 80% are of Black African origin
- 51% born outside the UK/Ireland
- 84% are on HAART (>10yrs)

**AT TRANSITION**

- Median age of transfer = 17.0 yrs (15.2-20.7)
- Median duration of follow up pre-transfer = 10yrs (IQR 6.2-14.9)
Numbers of children under care continues to increase

Workload of the Paediatric HIV Clinic
Weekly paediatric clinic

Manchester family clinic

- Adult ID consultant and SPR
- Paediatric Consultant(s)
- Adult clinical nurse specialists
- Paediatric clinical nurse specialist
- Paediatric pharmacist
- Paediatric dietician
- Play therapist
- Barnardo’s adolescent support group
- +/- Paediatric psychologist
- Separate testing clinic
Transitional vs Adolescent Service

- Transitional care is the planned movement of children with chronic health care problems from childrens’ to adolescent services
- Aim to achieve the best outcome for their long-term health
- Adolescence is the time when health is often compromised eg renal transplant rejection, worsening diabetic control
Transitional care could offer

- Motivational interviewing
- Safer sex advice
- STI testing and screening
- Psychological and social support
- Drug abuse prevention and services
- Contraception
- HPV and Hep B vaccination
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Thank you

For further information please contact:

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