MMed and DCH Lectures

Weekly by Zoom

Prof Trevor Duke

MMed and DCH Lectures

HIV in children and adolescents

May 11, 2020

Prof Trevor Duke

Aims of today's session

- Learn about HIV in children and adolescents
- Understand about types of ART, ART resistance, why children may fail treatment, and how to recognize and treat this.
- Chronic comorbidities in children and adolescents living with HIV

Case 1. Joseph: 10 year old boy with HIV

- Presented with cough 2 weeks
- HIV on ART for 4 years, adherent, very attentive father
- Severe muscle wasting, alert, no respiratory distress, scattered chest crepitations, no effusion. Painful lymph nodes in right groin, extreme tenderness over right shin.
- Sputum GeneXpert positive for MTB, Rifampicin sensitive

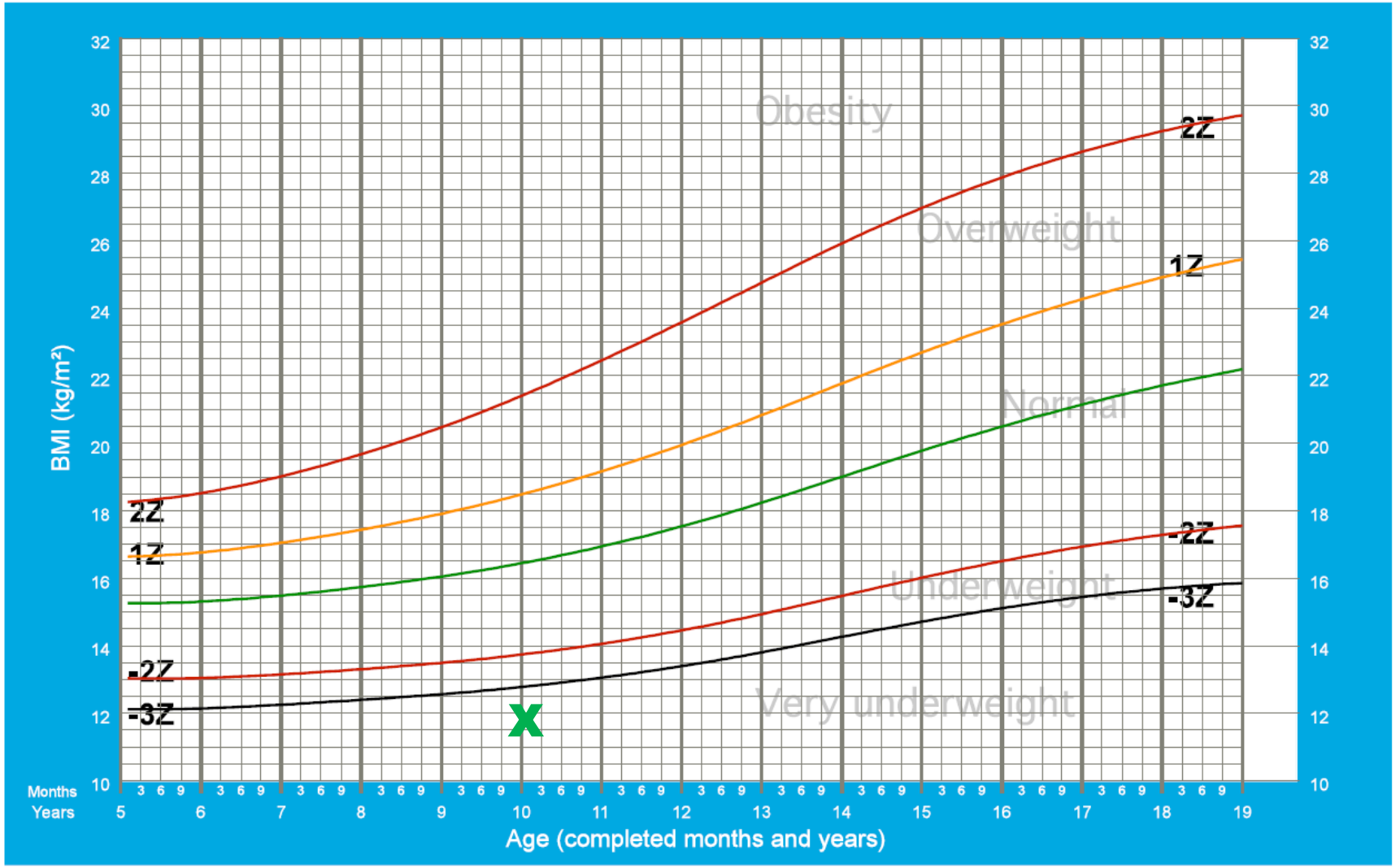
- What else do you want to know?
- Weight = 18.8kg

- Is his father on treatment? – No, he and the 2 other children are seronegative
- Is his mother on treatment? – She passed away last month
- What treatment was she on? The same as Joshua: AZT / 3TC / NVP

FBC

Haemoglobin	8.9 g/dl	(10.5 - 13.5)
Platelets	650 x 10^9/l	(150 - 400)
WCC	14.6 x 10^9/l	(6 - 18.0)
Neutrophils	12.0 x 10^9/l	(1.0 - 8.5)
Lymphocytes	0.8 x 10^9/l	(1.5 - 10.0)
MCV	65	(74 - 85)

Body mass index (BMI) for age: Boys (5–19 years of age, Z-scores)



For further information on the growth charts, please refer to: http://www.who.int/growthref/en/

https://pngpaediatricsociety.org/treatment/

BMI

$$\frac{\text{Weight (kg)}}{\text{Height}^2\text{ (m)}}$$

$$\frac{18.8\text{ kg}}{1.26\text{ m}^2}$$

BMI = 11.8

Current Infectious Disease Reports (2019) 21: 7
https://doi.org/10.1007/s11908-019-0663-z

PEDIATRIC INFECTIOUS DISEASES (I. BROOK, SECTION EDITOR)

Antiretroviral Resistance Patterns in Children with HIV Infection

J. Nuttall[1] · V. Pillay[1]

- High levels of resistance, particularly to non-nucleoside reverse transcriptase inhibitors (NNRTIs), and poor treatment outcomes on NNRTI-based 1st line ART among infants and young children.
- 354/1128 (31.3%) children had DRMs
- Median prevalence of NNRTI resistance was 49.3% (range 7.5–100%)
- 4/7 studies found > 50% of PMTCT-exposed children had NNRTI DRMs.

Pre-treatment drug resistance to NNRTIs

- 15-18% among newly diagnosed adults in PNG – likely higher among children.
- Many children on the wards clinically failing ART therapy still on Nevirapine-Lamivudine-Zidovudine (NVP/3TC/AZT) triple therapy

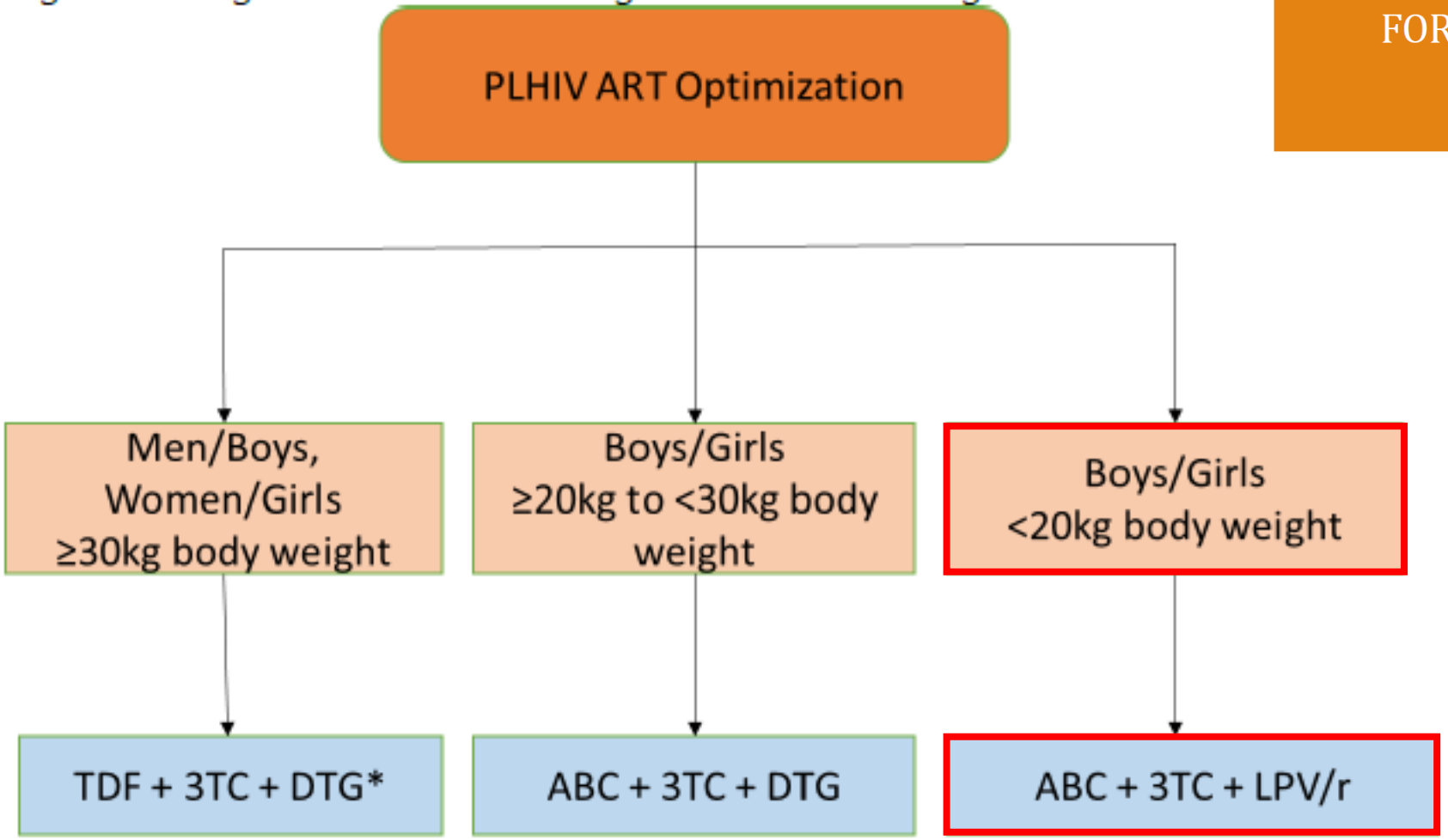
Classes of HIV drugs, and examples

1. NNRTI – non-nucleoside reverse transcriptase inhibitors (Nevirapine, Efavirenz)
2. NRTI – nucleoside reverse transcriptase inhibitors (Lamivudine, Zidovudine, Abacavir, Emtricitabine, Tenofovir)
3. PI – protease inhibitors (Lopinavir / ritonavir: “Kaletra”)
4. INSTI - Integrase strand transfer inhibitor (Raltegravir, Dolutegravir)

National Department of Health

PAPUA NEW GUINEA NATIONAL GUIDELINES FOR HIV CARE AND TREATMENT

Figure 1. Algorithm for choosing first-line ART regimen



PNG National Guidelines for HIV care and treatment: 2019

Types of ART resistance

- Acquired drug resistance – develops when HIV mutations emerge due to viral replication in individuals on ART
- Transmitted drug resistance – detected in ART drug naïve individuals, occurs when previously uninfected individuals become infected with virus that has drug resistance mutations (DRMs)
- Pre-treatment HIV drug resistance – detected in ARV drug-naïve individuals initiating ART

WHO resistance threshold

- A national pre-treatment resistance of >10% to an ARV drug or drug class: transition to a different first-line ART regimen.
- PDR is a strong predictor of treatment failure on first-line ART in infants and children, this has especially been shown with NNRTI DRMs.
- Some countries have regular surveillance for drug resistance that is performed on dried blood spots as part of early infant diagnosis (EID) testing in PMTCT programs.

Recommended second-line treatment?

- It depends on what the first-line therapy has been.
  a) If 1st line NNRTI based (Nevirapine or Efavirenz) then 2nd line therapy can either be:
     Integrase strand transfer inhibitor, such as Dolutegravir *plus* 2 NRTIs,
     or
     A Protease inhibitor such as Lopinavir/ritonavir plus 2 NRTIs
  b) If it has been a PI-based first-line therapy, then WHO suggests Raltegravir *or* Dolutegravir plus 2 NRTIs.

When to change from first-line therapy to *second-line* therapy?

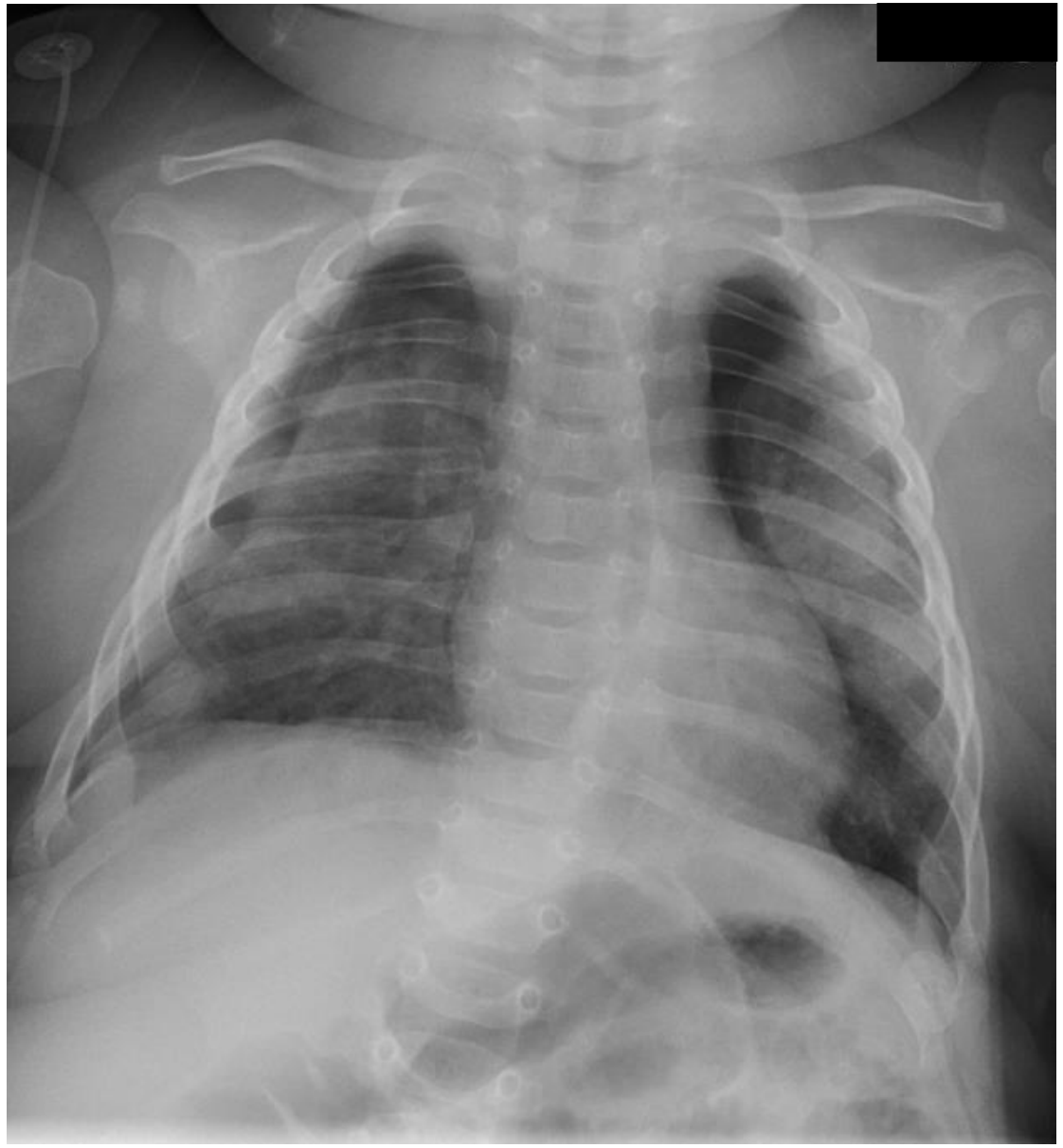
- **Viral failure**: persistently detectable viral load >1000 copies/mL (2 consecutive viral load measurements 3-months apart with adherence support between measurements), after 6 months of starting a new ART regimen.
- **Immunological failure**: <5 years: Persistent CD4 levels <200 cells/mm3; >5 years: Persistent CD4 levels <100 cells/mm3.
- **Clinical failure:** New or recurrent clinical event indicating advanced or severe immunodeficiency (WHO clinical stage 3 and 4 clinical condition with the exception of TB) after 6 months of effective treatment

CD-4 T-cell lymphocytes

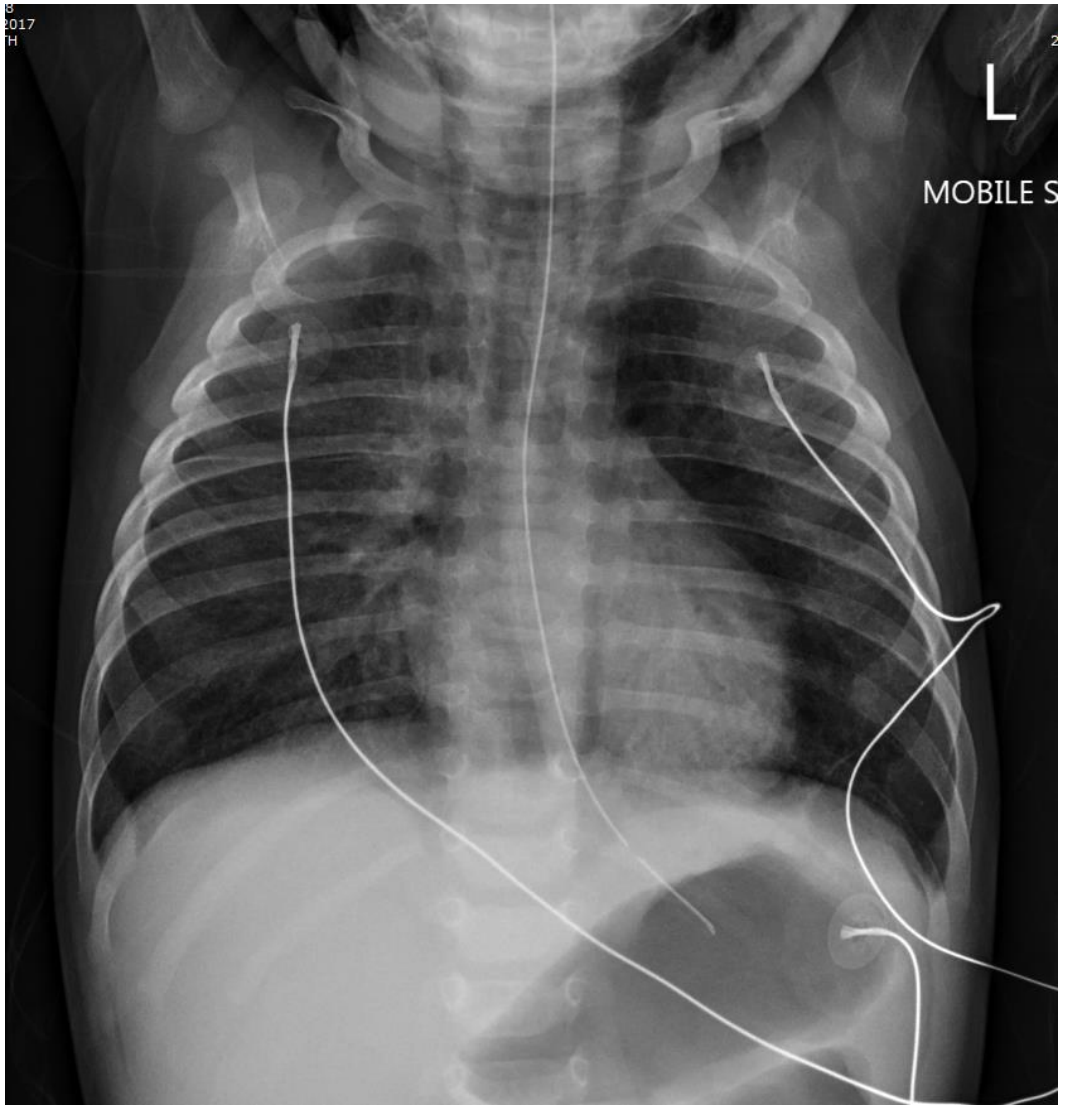
Age	Normal / mild immune suppression CD4 cells/µl	Moderate immune deficiency CD4 cells/µl	Severe immune deficiency CD4 cells/µl
Infants	>1500	750-1499	<750
1-5 years	>1000	500–999	<500
6-12 years	>500	200-499	<200

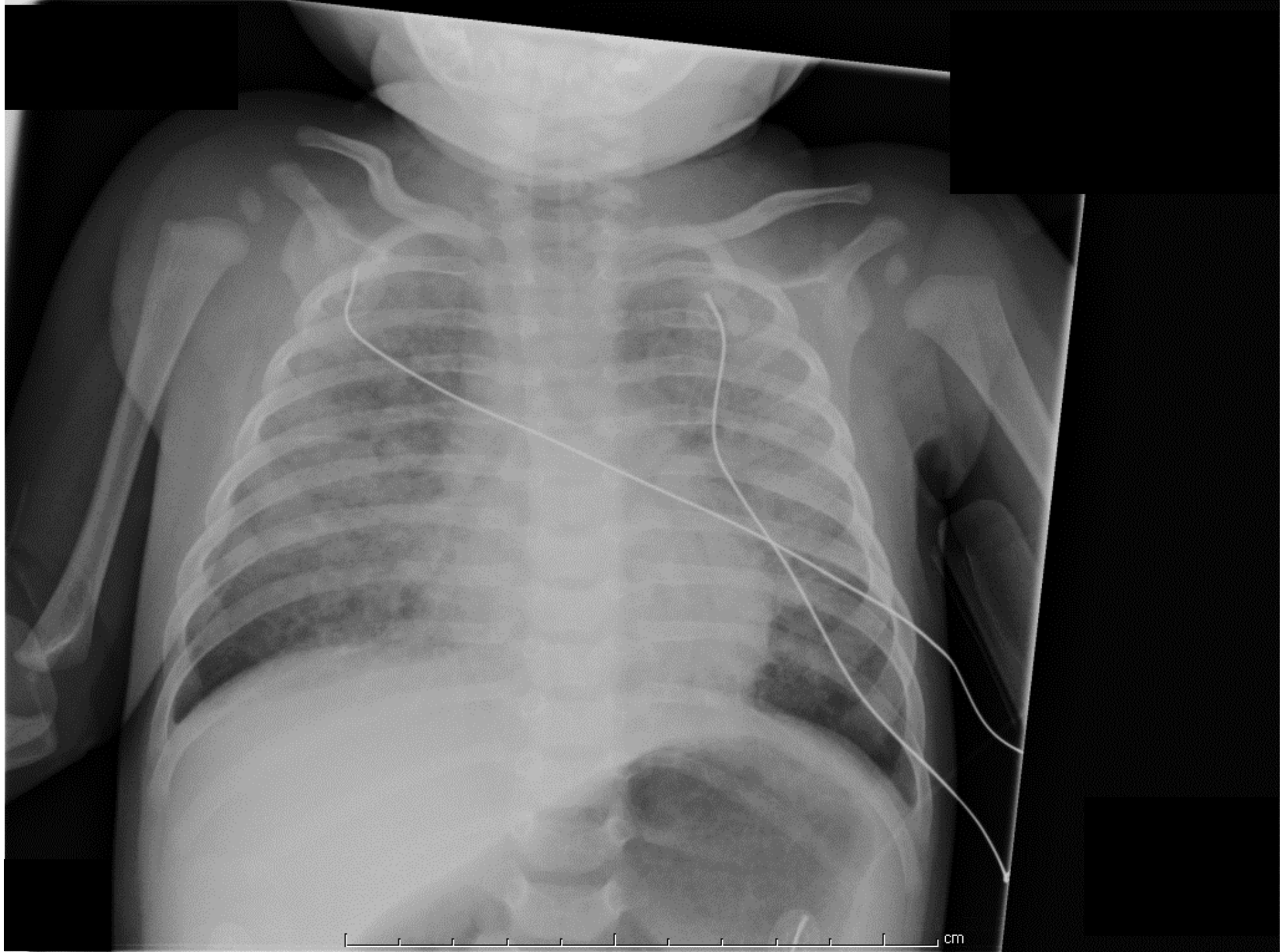
Case 2.

- 5 month old girl, presents with severe respiratory distress
- “HIV-exposed”
- What do you want to know?
- Awaiting “DBS” result
- On 6 weeks of AZT/NVP, then NVP until 4 months of age
- What do you think?



- Improved on high-dose cotrimoxazole
- Air-leak, think pneumocystis
- PjP can improve within 48 hours of starting treatment, other infections tend to take longer (TB)
- What ART should she be on?




cm

PPTCT

National Department of Health

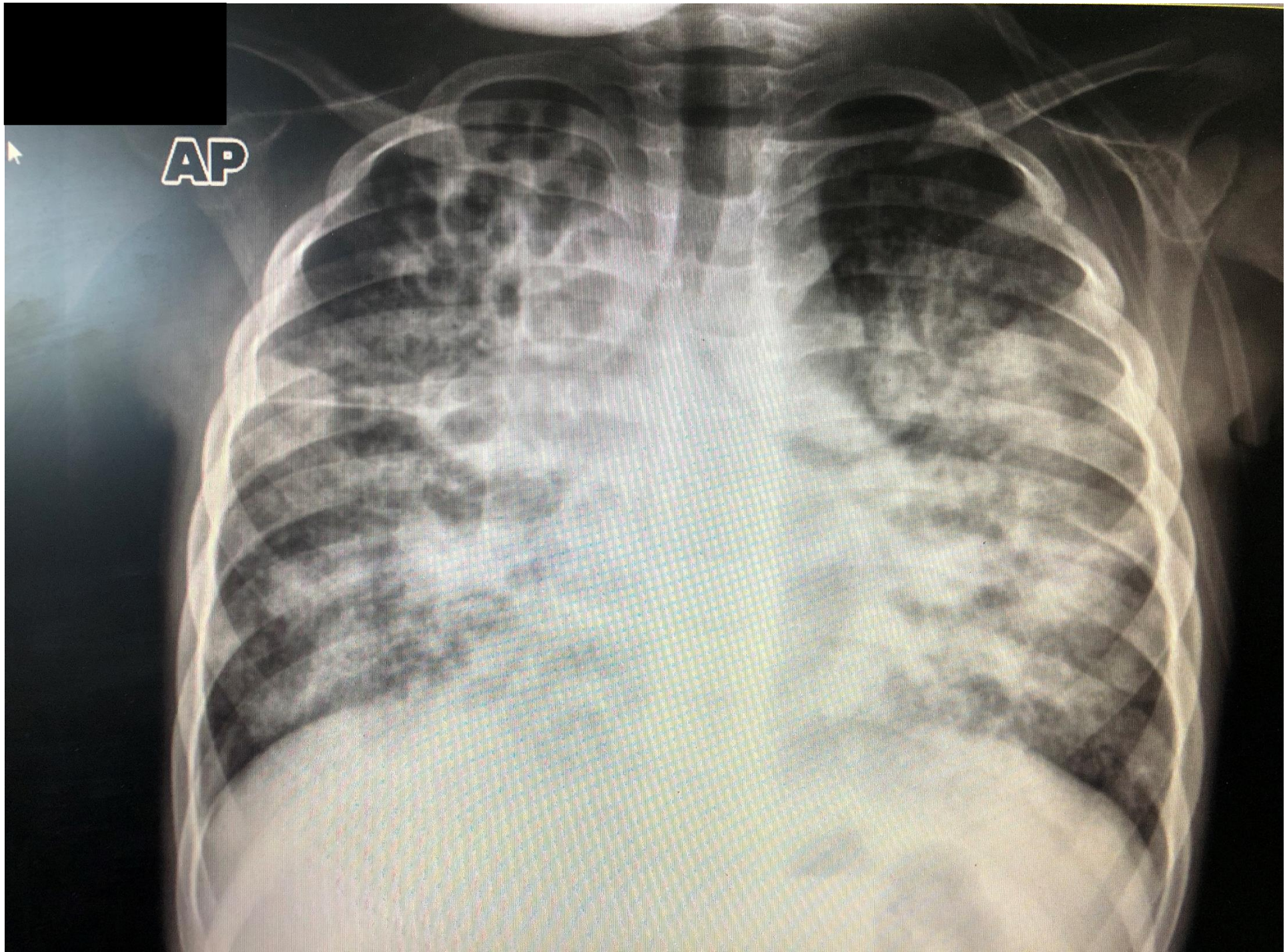
PAPUA NEW GUINEA NATIONAL GUIDELINES FOR HIV CARE AND TREATMENT

ARV prophylaxis for Infants at High Risk of MTCT	**ARV prophylaxis for Infants at Low Risk of MTCT**
AZT and NVP for **the first 6 weeks** of life **+** **NVP only for an additional 6 weeks** **Total 12 weeks**	**NVP only** for the first **6 weeks** of life **Total 6 weeks**

Chronic comorbidities in children and adolescents with perinatally acquired HIV infection in sub-Saharan Africa in the era of antiretroviral therapy

Lisa J Frigati, Wole Ameyan, Mark F Cotton, Celia L Gregson, Jacqueline Hoare, Jennifer Jao, Edith D Majonga, Landon Myer, Martina Penazzato, Ruramayi Rukuni, Sarah Rowland-Jones, Heather J Zar, Rashida A Ferrand

- More common now that children are surviving on ART
- Late commencement of effective ART a risk


AP

Chronic comorbidities: chronic lung disease

- Chronic bronchitis, bronchiectasis
- Obliterative bronchiolitis
  - Airflow obstruction (FEV1), inflammation and dense fibrous scarring of bronchiolar epithelium
- Some will be post-viral (adenovirus), post-TB + chronic bronchitis + immune deficiency
- Management
  - Keep colonising bacteria from flaring up – cotrimoxazole / azithromycin
  - Vaccines (PCV, influenza)
  - Nutrition
  - Avoid smoking, air pollution
  - Bronchodilators (partially effective)
  - Diuresis
  - Avoid steroids
  - Oxygen
  - Pulmonary hypertension (sildenafil)

Cardiovascular comorbidities

- Cardiac
  - Left ventricular systolic and diastolic dysfunction
  - Left ventricular hypertrophy
  - Cardiac conduction detects
  - Pericardial thickening
- Vascular
  - Premature atherosclerosis – Protease inhibitors (PI)

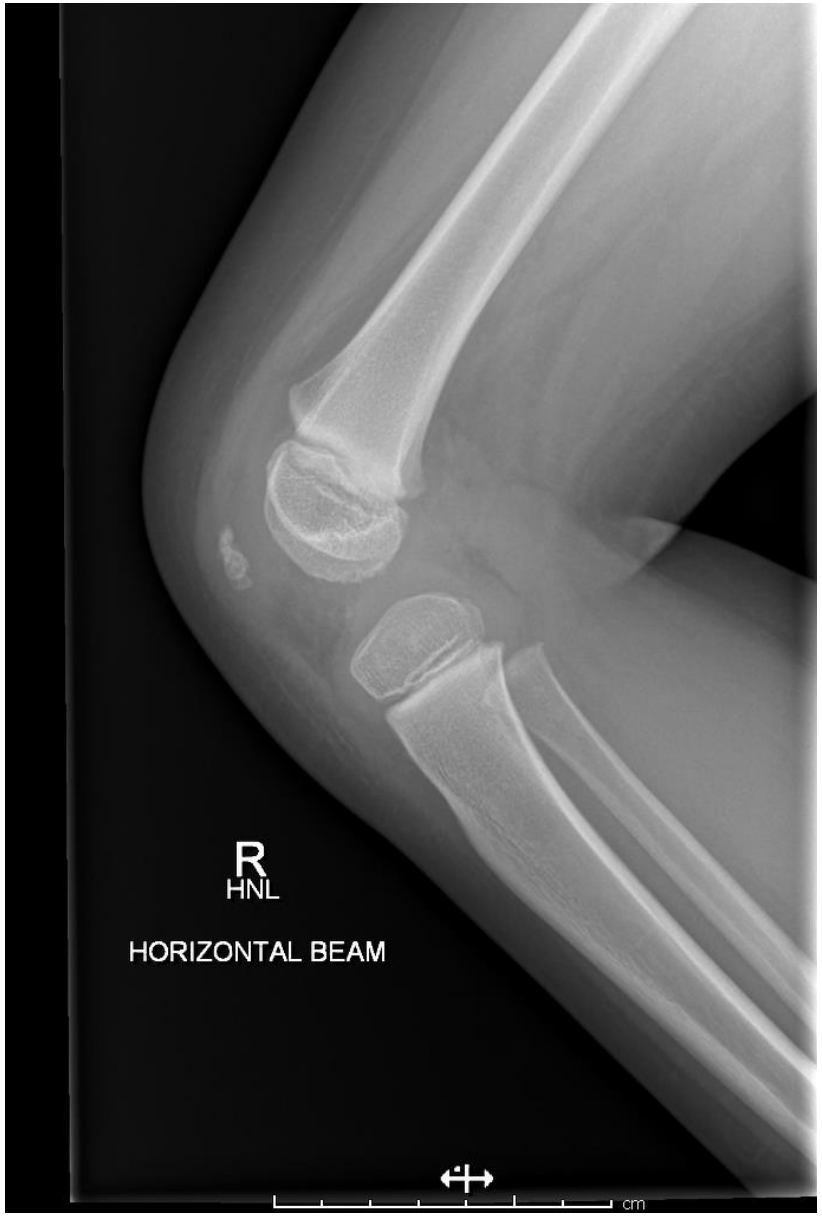
Renal and metabolic disease

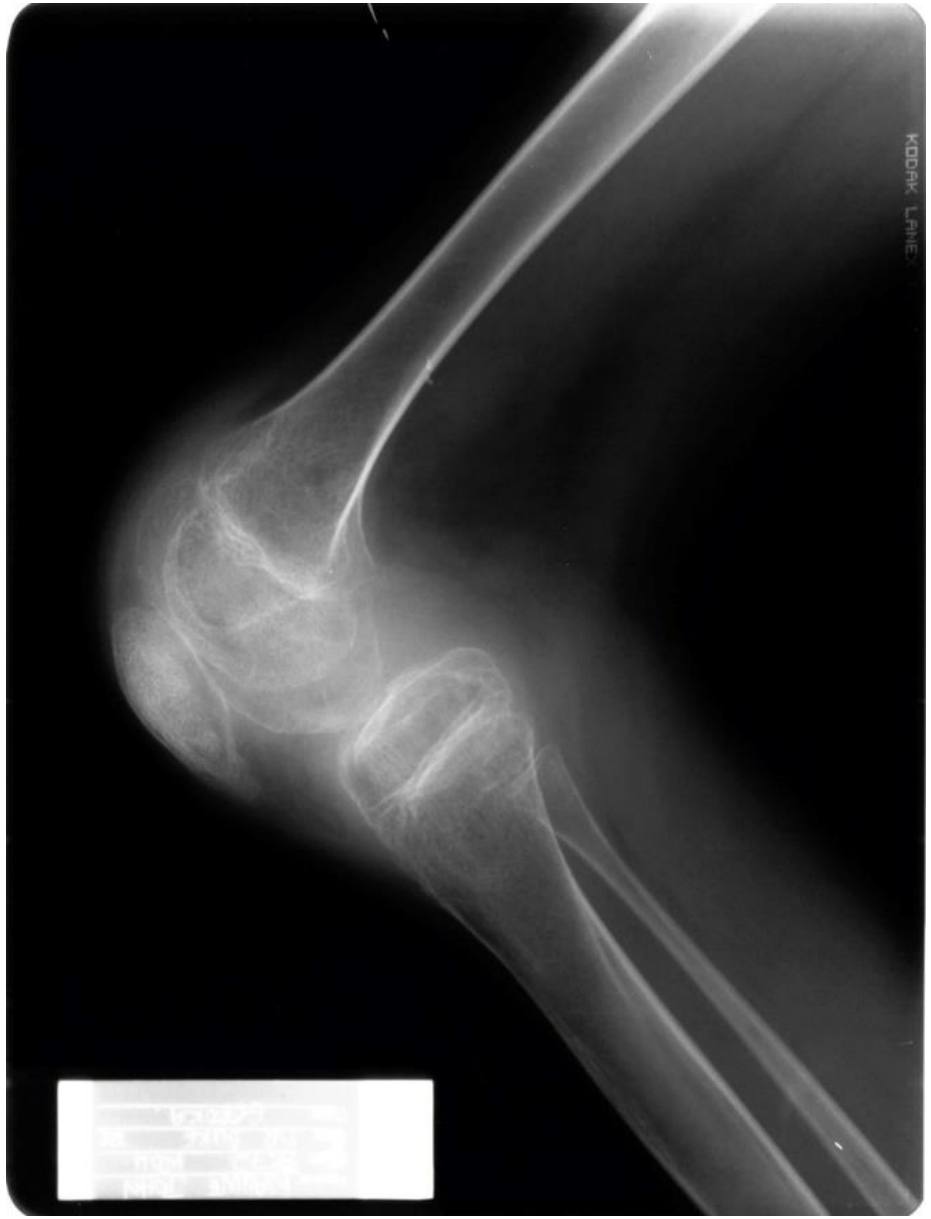
Renal

- Glomerular injury – microalbuminuria
- Renal tubulopathy (loss of protein, phosphate, glucose)
- Tenofovir

Metabolic

- Lipodystrophy
- Insulin resistance


R
HNL
HORIZONTAL BEAM
cm


KODAK LANE

Musculoskeletal

- Stunting
- Low bone density
  - Inadequate daily calcium intake, vitamin D deficiency, pro-inflammatory state
  - Poor muscle strength – lack of impact load on bones, therefore bone accumulation / development poor
  - Tenofovir accelerates bone loss
  - Fracture risk

Neurological

- Many factors effect brain development in HIV
  - Virus replication in CNS and inflammation – irreversible injury before ART established
  - Neurotoxic effects of ART
  - Nutrition and micronutrient - e.g. breast feeding and myelination
  - Psychosocial factors – stigma, discrimination, lack of schooling, responsibility for siblings, unstable guardianship, lack of early life opportunity to learn

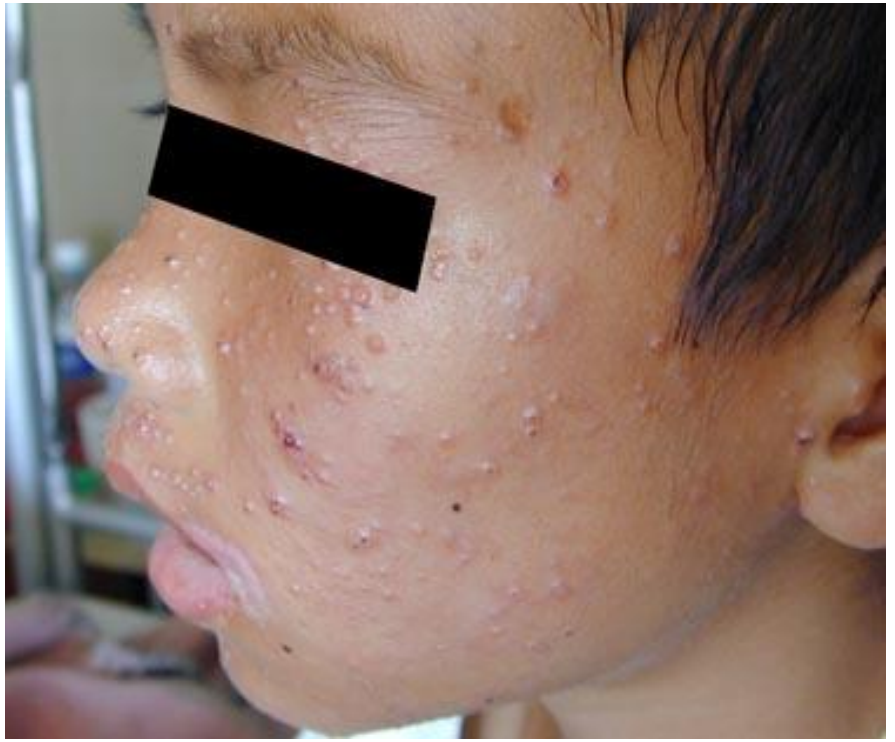
Malignancy

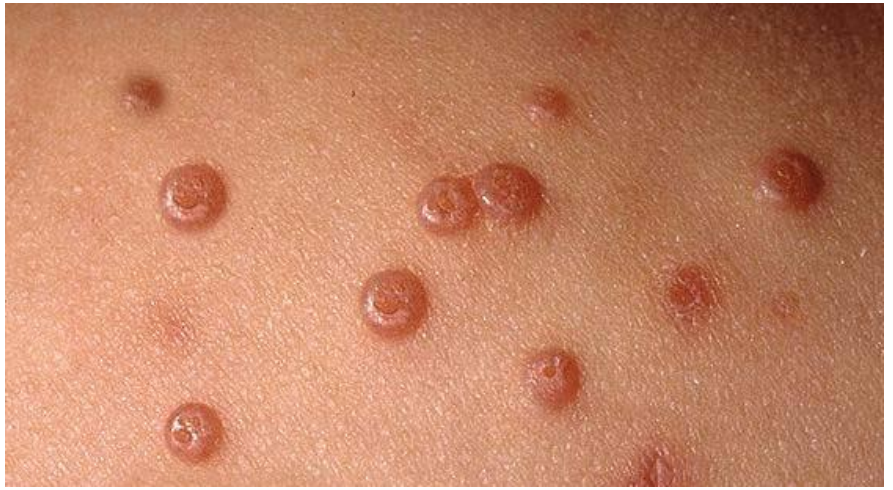
- Kaposi sarcoma
- Non-Hodgkin lymphoma
- Cervical cancer from HPV

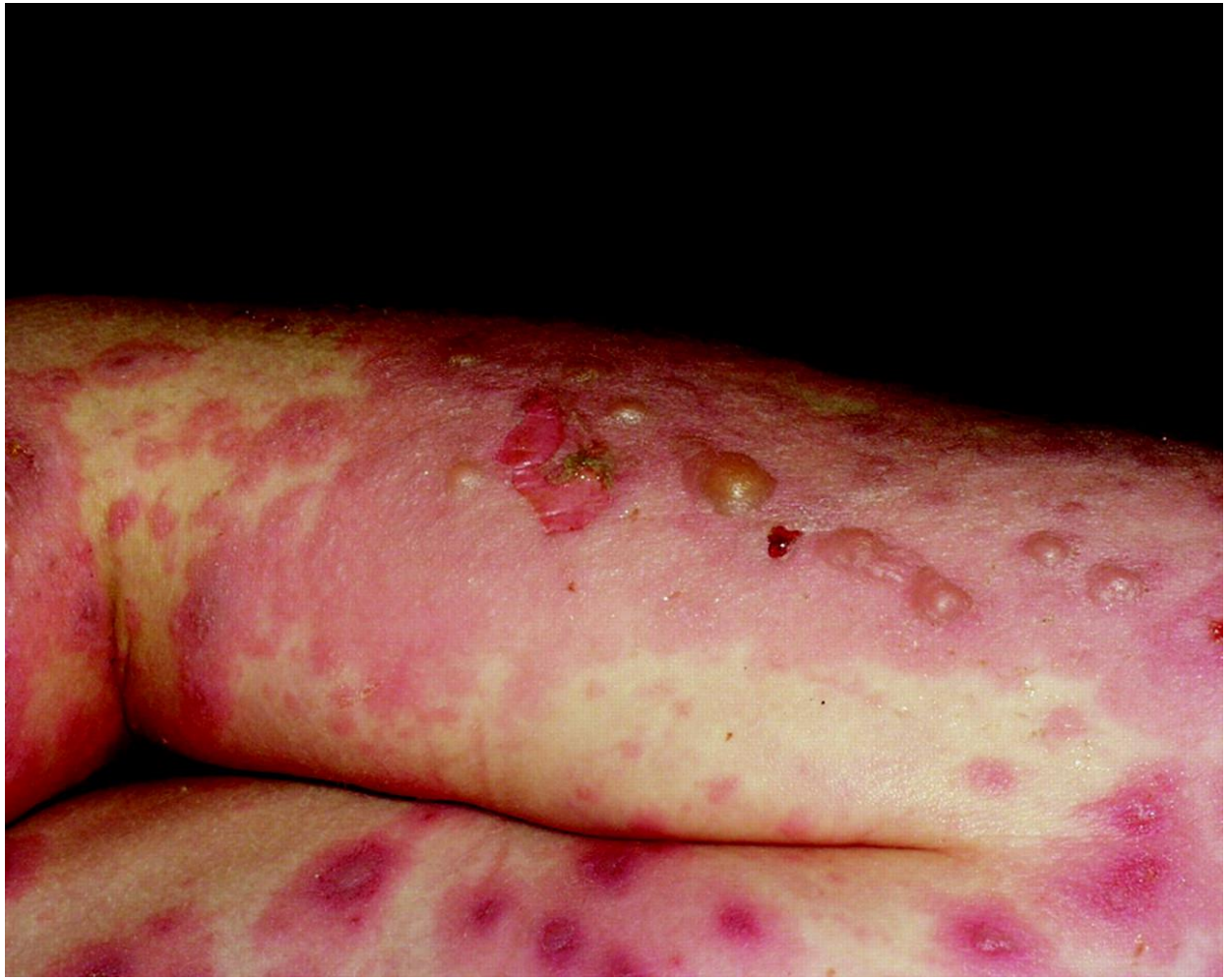
- All reduced by effective ART

Skin

- Skin rashes often severe and widespread
  - Molluscum contagiosum
  - Seborrheic dermatitis
  - Plantar warts
- Drug reactions - SJS
- Reconstitution immune syndrome (unmasking an underlying skin problem when immune reconstitution occurs after ART begins)



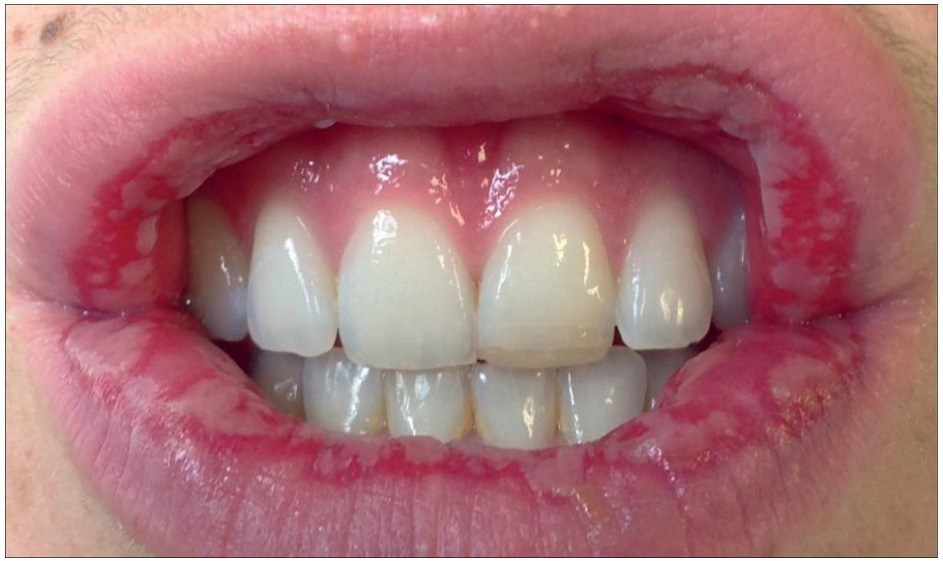




Medications as Risk Factors of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children: A Pooled Analysis. Pediatrics 2009, 123 e297-e304

Stevens-Johnson Syndrome in HIV

- Nevirapine
- Suphonamides
- AEDs



Erythema multiforme major with swollen lips and crusted erosions. Lancet 2018; 392: 592

Chronic comorbidities in children and adolescents with perinatally acquired HIV infection in sub-Saharan Africa in the era of antiretroviral therapy

Lisa J Frigati, Wole Ameyan, Mark F Cotton, Celia L Gregson, Jacqueline Hoare, Jennifer Jao, Edith D Majonga, Landon Myer, Martina Penazzato, Ruramayi Rukuni, Sarah Rowland-Jones, Heather J Zar, Rashida A Ferrand

- Dysregulated immune system
- Gut translocation
  - malnutrition, chronic diarrhoea, CMV infection of GI mucosal epithelium
- Inflammation
- Infection with HIV virus
- Drug-side effects

Monitoring of children with HIV

- 6 monthly CD4 or viral load
- Disclosure
- Adherence and encouragement
- Vaccines
- School participation, self esteem, mental health
- Nutrition and development
- Mitigation of chronic comorbidities
- Drug side effects