MMed and DCH Lectures

HIV in children and adolescents

August 30, 2021

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

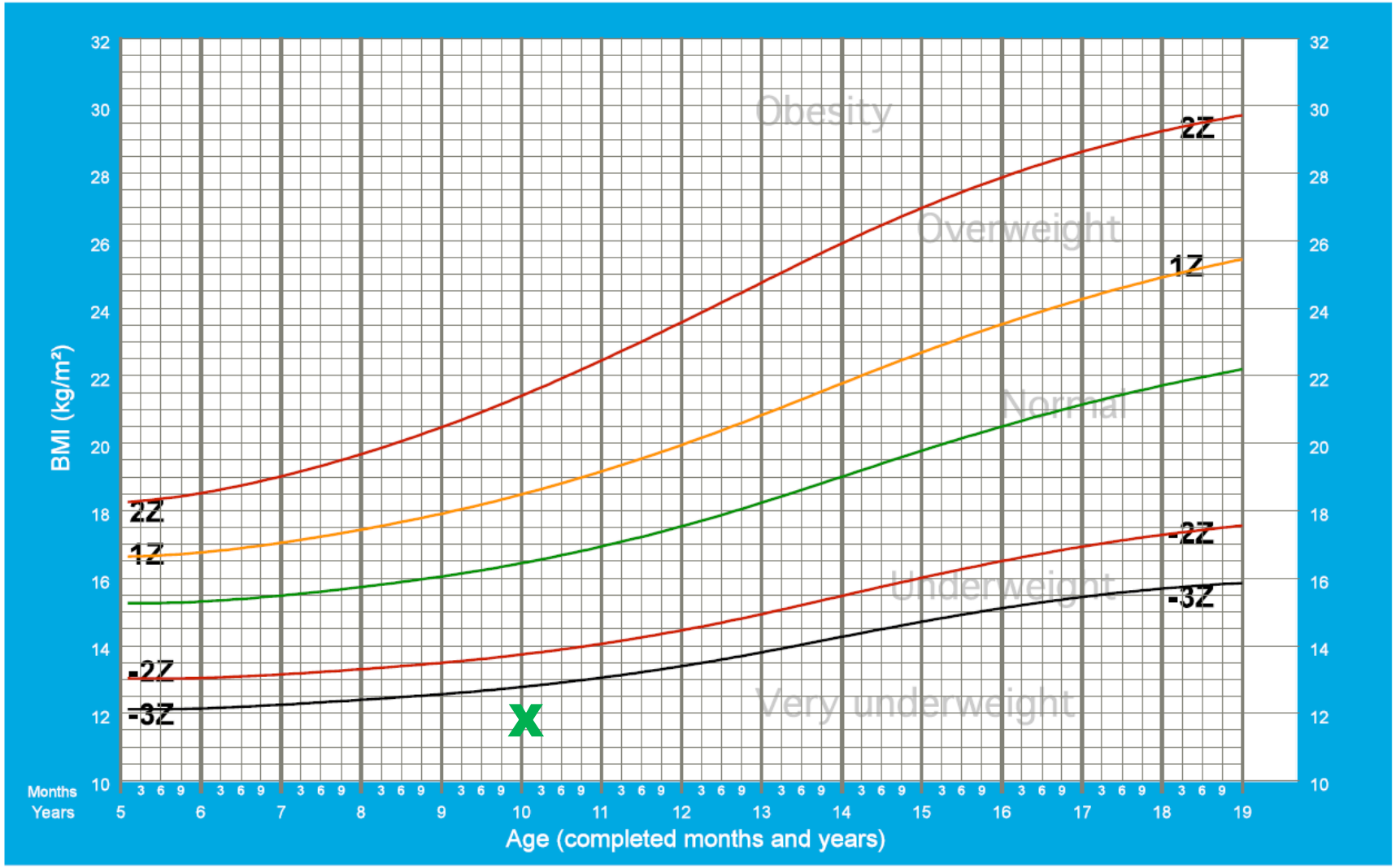
- What else do you want to know?
- Weight = 18.8kg

- 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

RESEARCH ARTICLE

High Levels of Transmitted HIV Drug Resistance in a Study in Papua New Guinea

Evelyn Lavu[1], Ellan Kave[1], Euodia Mosoro[1], Jessica Markby[2], Eman Aleksic[2], Janet Gare[2,3], Imogen A. Elsum[2], Gideon Nano[4], Petronia Kaima[5], Nick Dala[4], Anup Gurung[6], Silvia Bertagnolio[7], Suzanne M. Crowe[2], Mark Myatt[8], Anna C. Hearps[2☯], Michael R. Jordan[9,10☯*]

PLOS ONE | DOI:10.1371/journal.pone.0170265 February 1, 2017

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)

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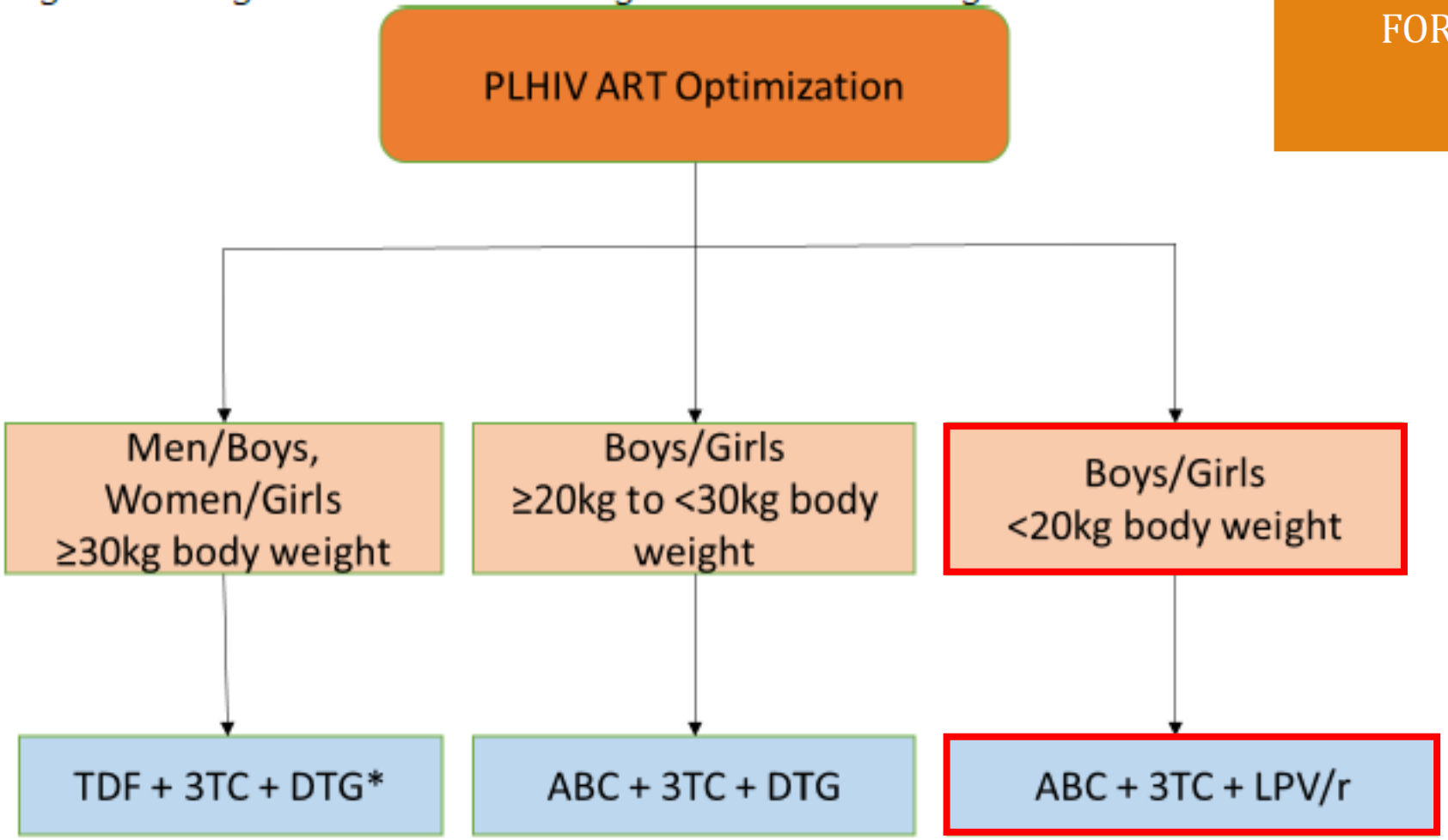
PAPUA NEW GUINEA NATIONAL GUIDELINES FOR HIV CARE AND TREATMENT

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 person on ART
- Transmitted drug resistance – detected in ART drug naïve individuals, occurs person become infected with a 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:
   (i) Protease inhibitor: **Lopinavir/ritonavir** plus 2 NRTIs (ABC/3TC/LPVr)
   (ii) Integrase strand transfer inhibitor, e.g. **Dolutegravir** plus 2 NRTIs (ABC/3TC/DTG)

b) If *already* on a PI-based first-line therapy
   WHO recommends Dolutegravir plus 2 NRTIs (ABC/3TC/DTG)

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

Viral load testing

- Viral load test: 6 and 12 months after initiation of ART and every 12 months thereafter.
- For children on NNRTI-based regimens: switch ART at the first unsuppressed viral load test result (do not follow the routine adherence interventions and repeat viral load after 3 months as recommended if the child is on a DTG-based or PI-based regimen and has an unsuppressed viral load).

- **WHO new guidelines**
  1st and 2nd line ART for all children >4 weeks (≥3Kg): DTG-based regimens
- The preferred regimen for a child/adolescent 30 Kg and above: TDF +3TC + DTG.

Table 1. Summary of preferred and alternative first-line ART for neonates and children

	Neonates	Children
Preferred	AZT+3TC+RAL[a]	ABC + 3TC + DTG
Alternatives	AZT+3TC+NVP	ABC + 3TC + LPVr TAF[c] + 3TC (or FTC) + DTG ABC + 3TC + RAL[d]
Special circumstances[d]	AZT+3TC+LPVr[b]	ABC + 3TC + EFV[e] (or NVP[f]) AZT + 3TC + EFV[e] (or NVP[f]) AZT + 3TC + LPVr (or RAL)

Dolutegravir-based therapy (*Tivicay*)

- 2018: recommended by WHO
- ALL infants and children (>4 weeks and at least 3 kg) established on 1st and 2nd line ART should be rapidly transitioned to DTG-based regimens irrespective of their current regimen.
- Viral load testing not a precondition. Children should not have their transition to DTG delayed due to lack of documented viral load.
- DTG high genetic barrier to drug resistance
- Child formulation: 10mg dispersible tablet

What treatment should Joseph be on?

TDF/3TC/DTG

Or

ABC/3TC/DTG

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

IRIS: Immune Reconstitution Inflammatory Syndrome

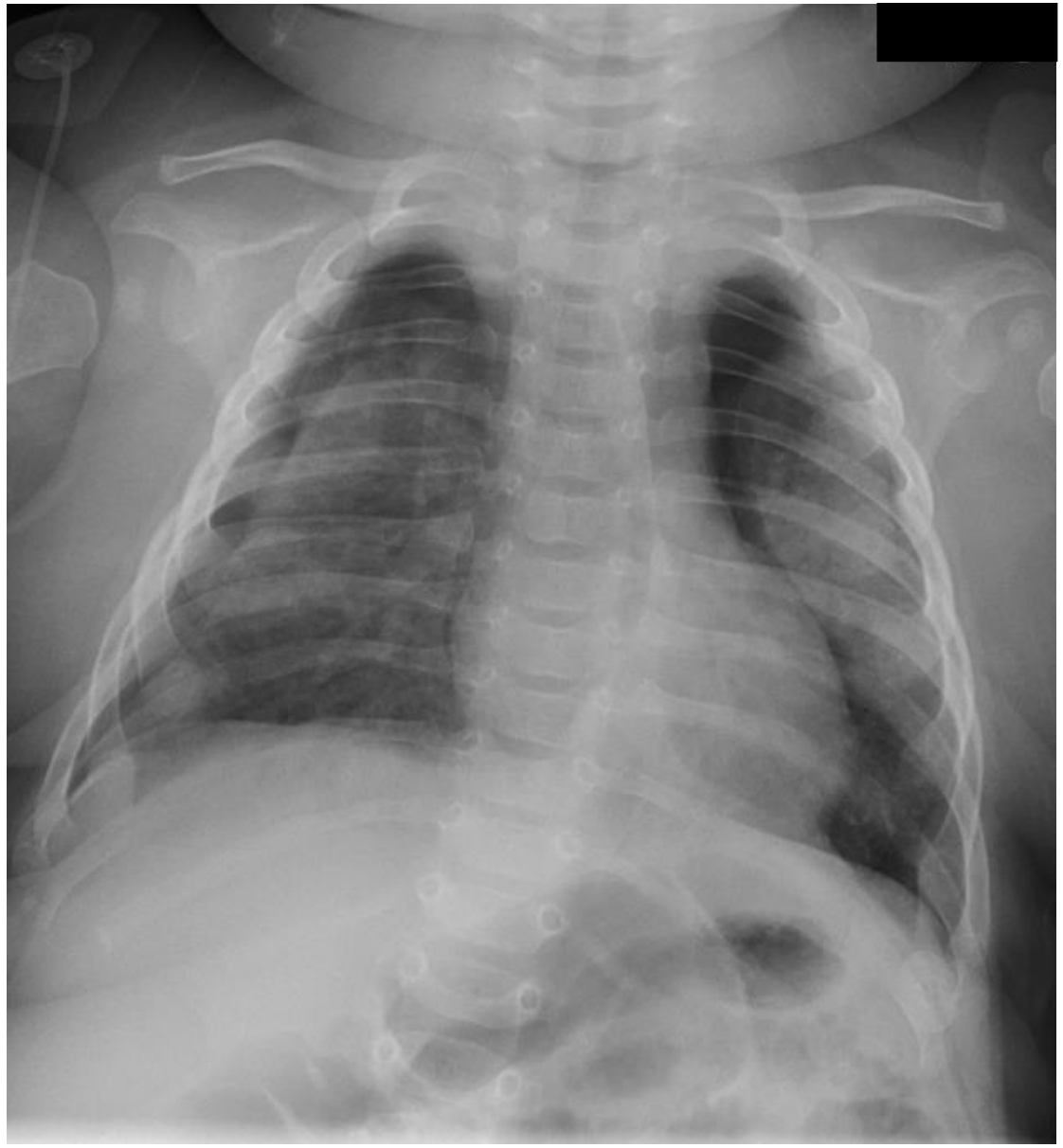
- Paradoxical clinical deterioration despite good immunological and virological response to antiretroviral therapy.
- It is due to the improving immune system recognising and mounting an immune response to organisms that have infected the body during the early stages of HIV infection.
- First 6 weeks after starting ART
- Clinical features depend on the causative organism and the organ system that is infected
- IRIS caused by MTB: high fever, lymphadenopathy, worsening of the original TB lesion, deteriorating chest x-ray (such as development of a miliary pattern or pleural effusion)

Infections that can manifest as IRIS

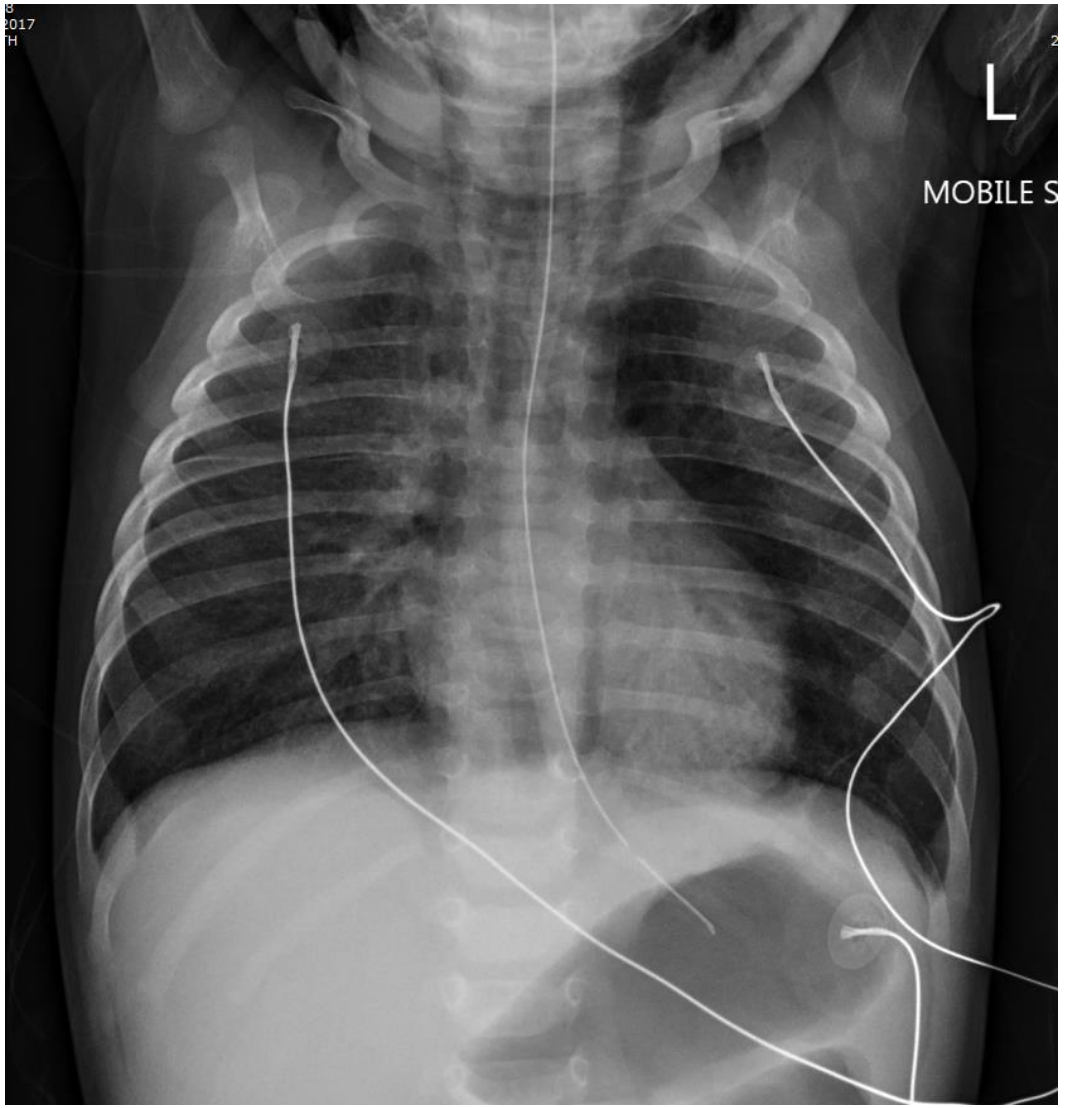
- Mycobacterium tuberculosis (MTB)
- Mycobacterium Bovis (BCG)
- Herpes simplex virus
- Mycobacterium avium complex
- Mycobacterium leprae
- Cryptococcus neoformans
- Aspergillus
- Candida
- Pneumocystis carinii
- CMV, HPV, Hepatitis B and C viruses (HBV, HCV)

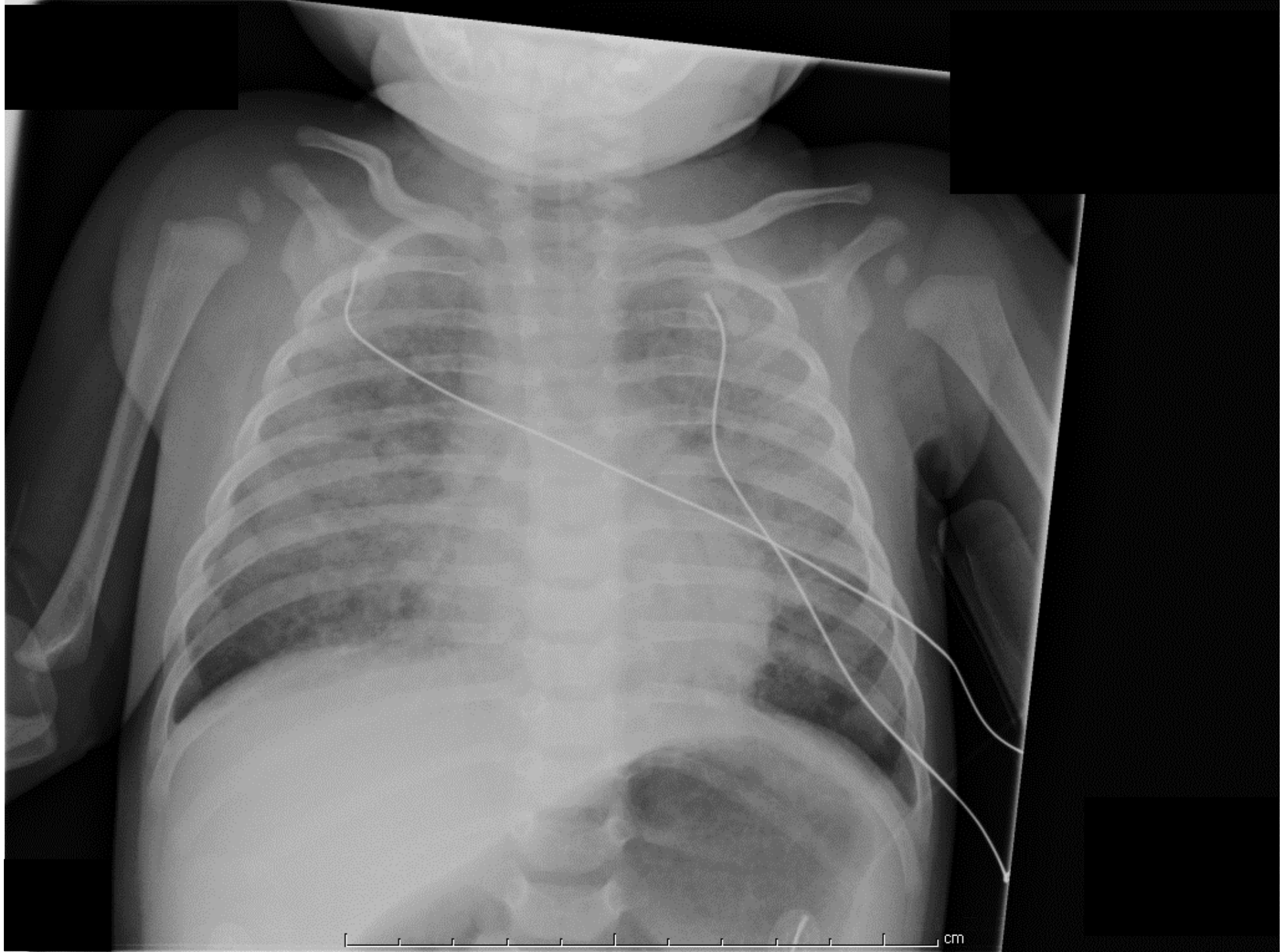
Case 2.

- 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?

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PPTCT

National Department of Health

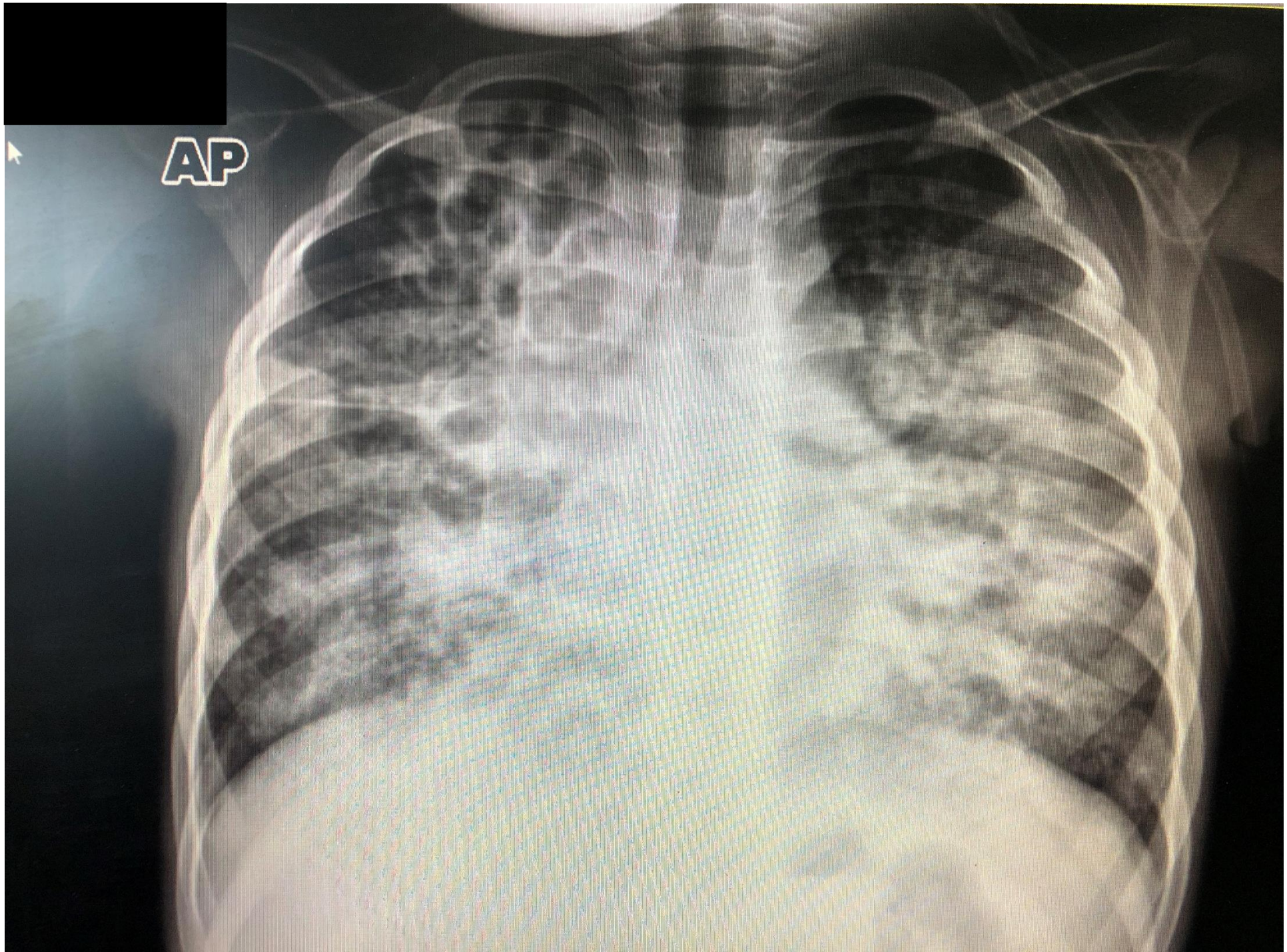
PAPUA NEW GUINEA NATIONAL GUIDELINES FOR HIV CARE AND TREATMENT

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)

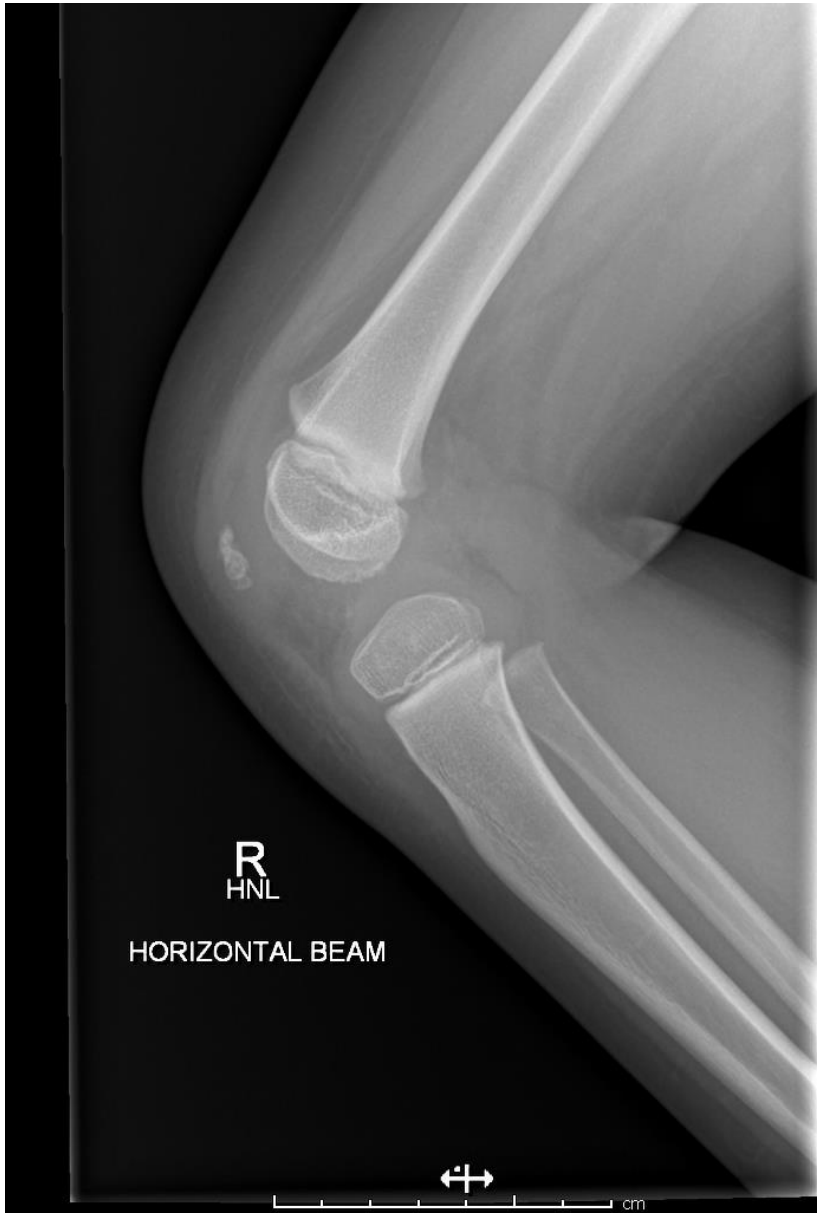
Renal and metabolic disease

Renal

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

Metabolic

- Lipodystrophy
- Insulin resistance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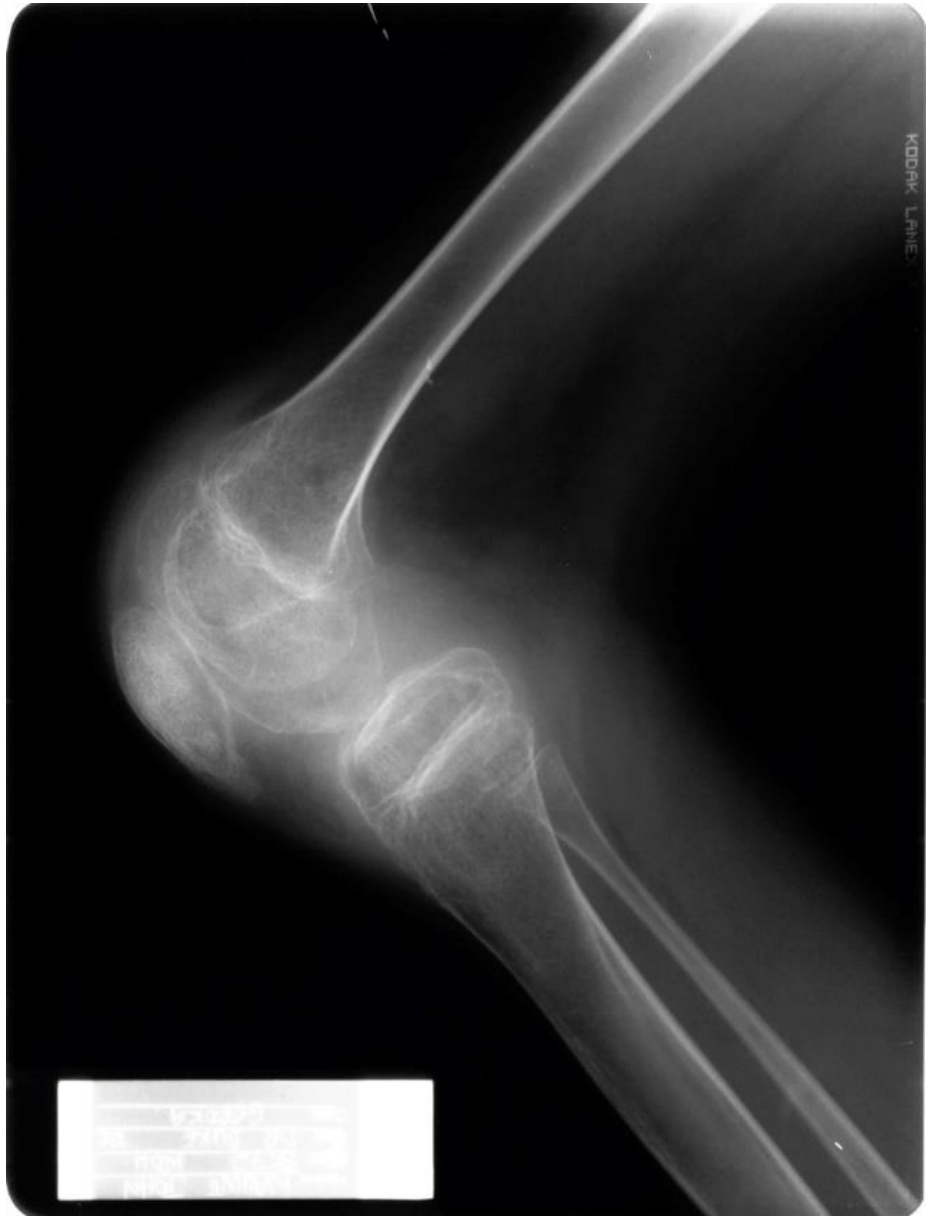

KODAK LANE

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

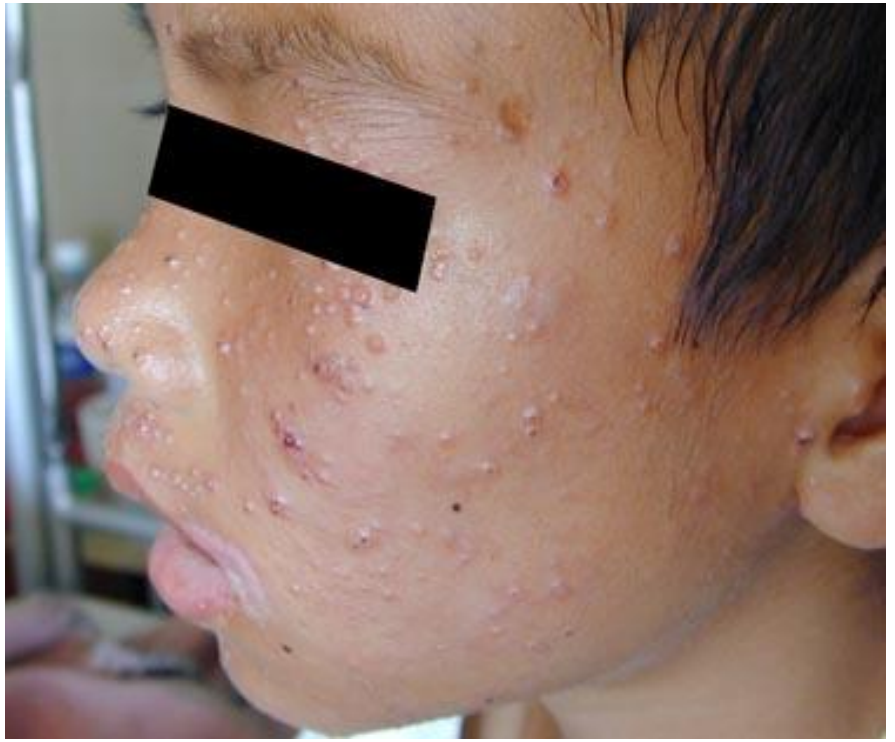
Malignancy

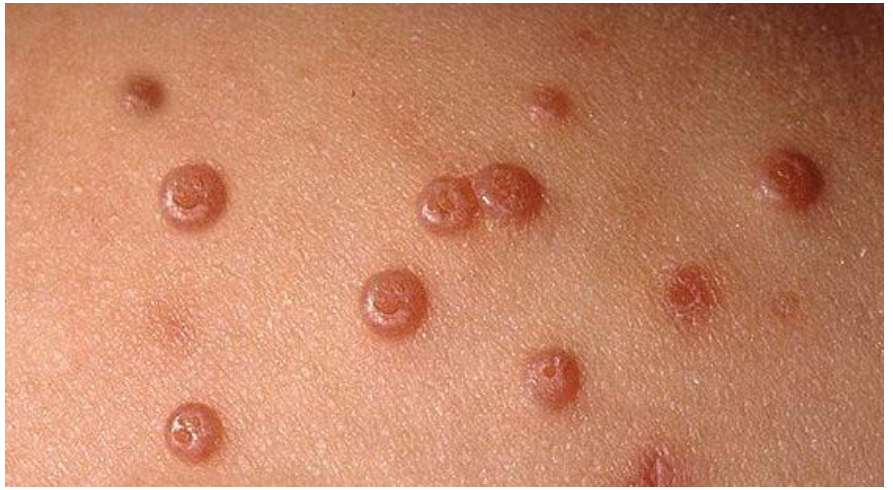
- Kaposi sarcoma
- Non-Hodgkin lymphoma
- Cervical cancer from HPV

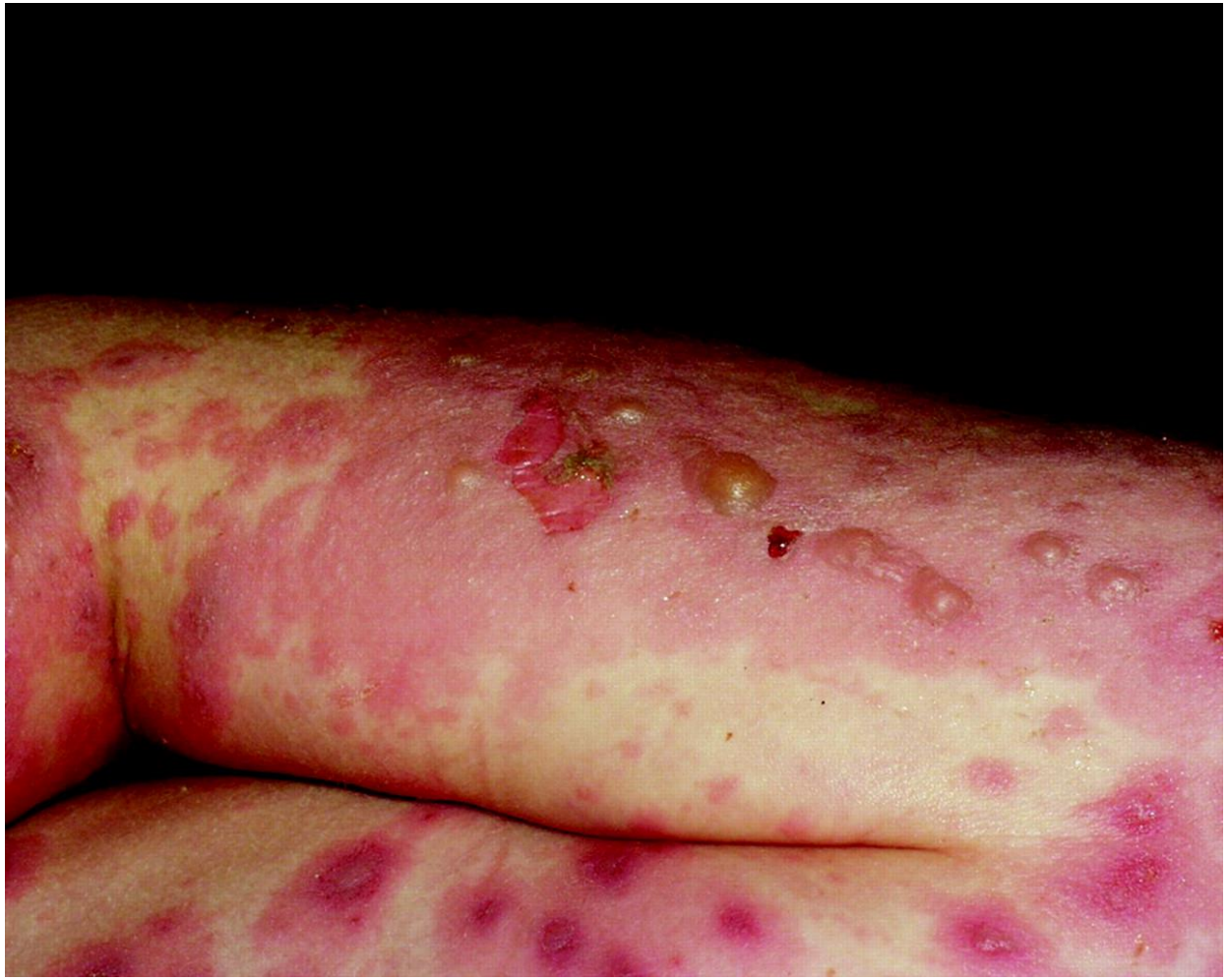
- All reduced by effective ART

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)



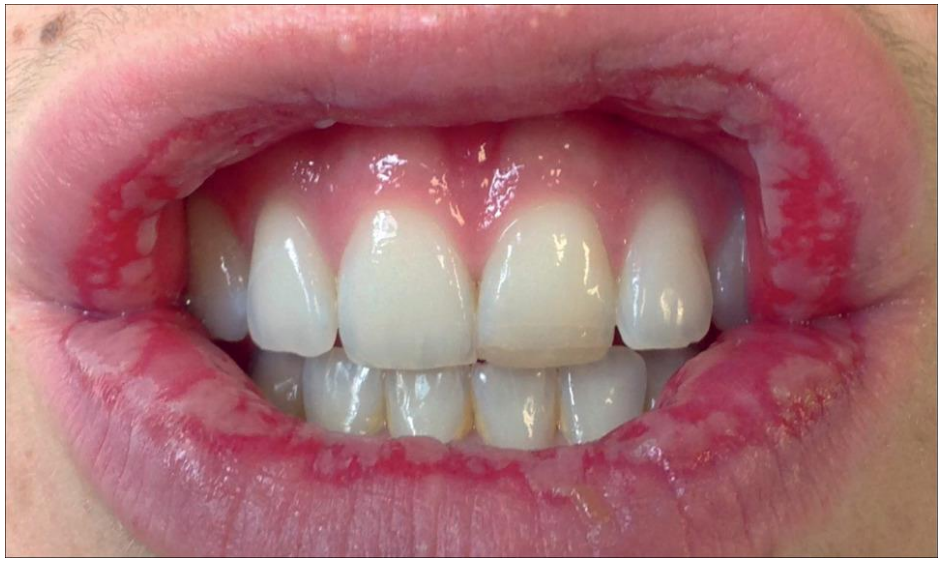




Medications as Risk Factors of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis in Children: A Pooled Analysis. Pediatrics 2009, 123 e297-e304

Stevens-Johnson Syndrome in HIV

- Nevirapine
- Suphonamides
- AEDs



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

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- 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

	ART Regimen	What to do when TB treatment is started
Neonates	RAL-based*	Dose adjustment needed: See dosing annex
	NVP-based	Change of regimen needed: NVP to be substituted as soon as possible with DTG or LPVr (with appropriate dose adjustment).
Children	DTG-based regimen*	Dose adjustment needed: See dosing annex
	LPVr-based regimen	Transition to DTG-based regimen (with appropriate dose adjustment) is preferable, where not possible LPVr dose adjustment is needed
	RAL-based regimen	Transition to DTG-based regimen (with appropriate dose adjustment) is preferable, where not possible RAL dose adjustment is needed
	TAF-containing regimen	Change of regimen needed: TAF to be substituted with ABC or TDF
	ATVr-based regimen	Change of regimen needed: replace ATVr with DTG if DTG naïve, with LPVr if DTG experienced
	DRVr-based regimen	Change of regimen needed: replace DRVr with DTG if DTG naïve, with LPVr if DTG experienced