Paediatric HIV update

Dr Gamini Vali –Boma

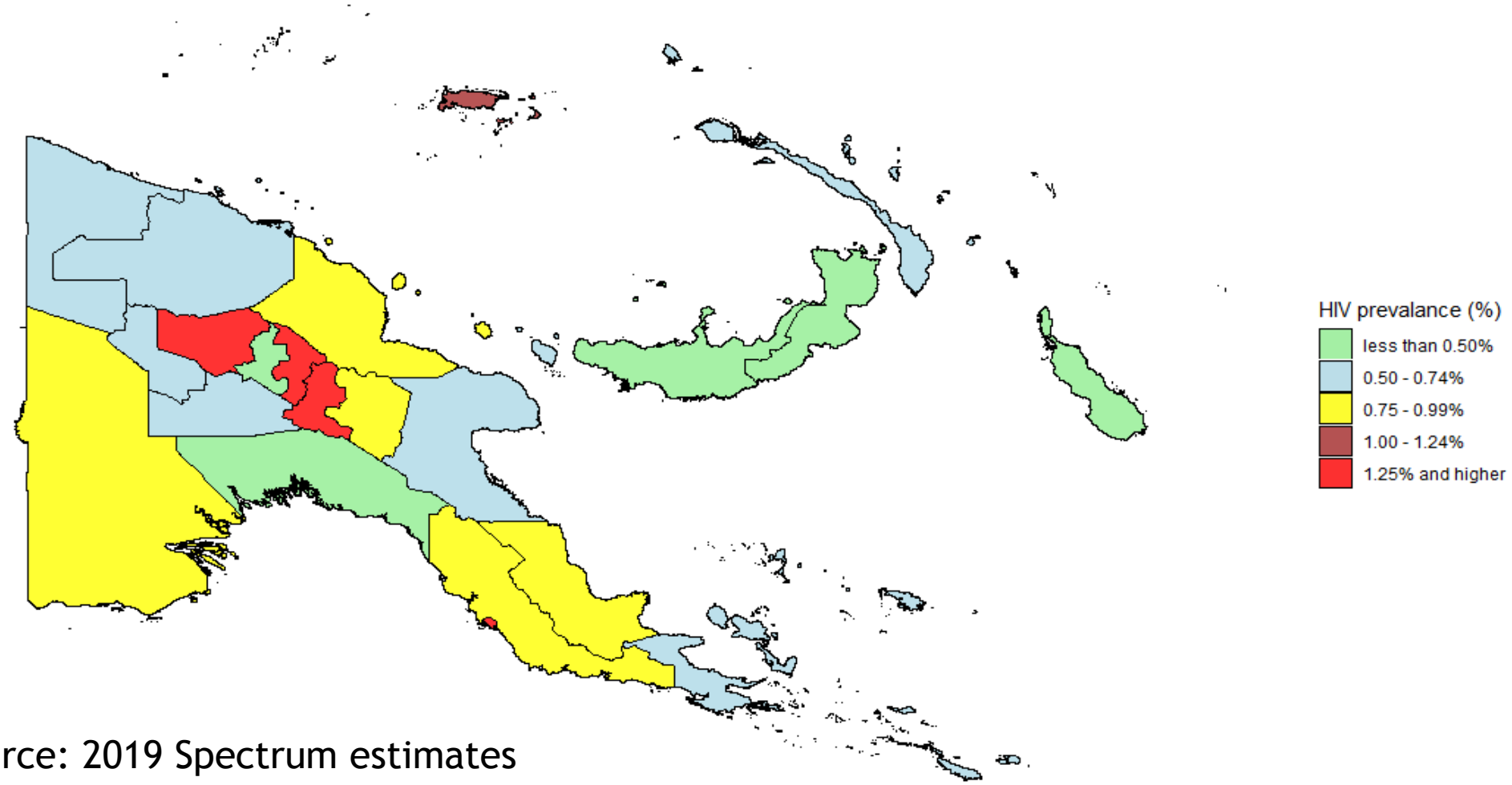
Paediatric Society Symposium (28th -30th August 2019)

School Of Medicine and Health Sciences

Introduction

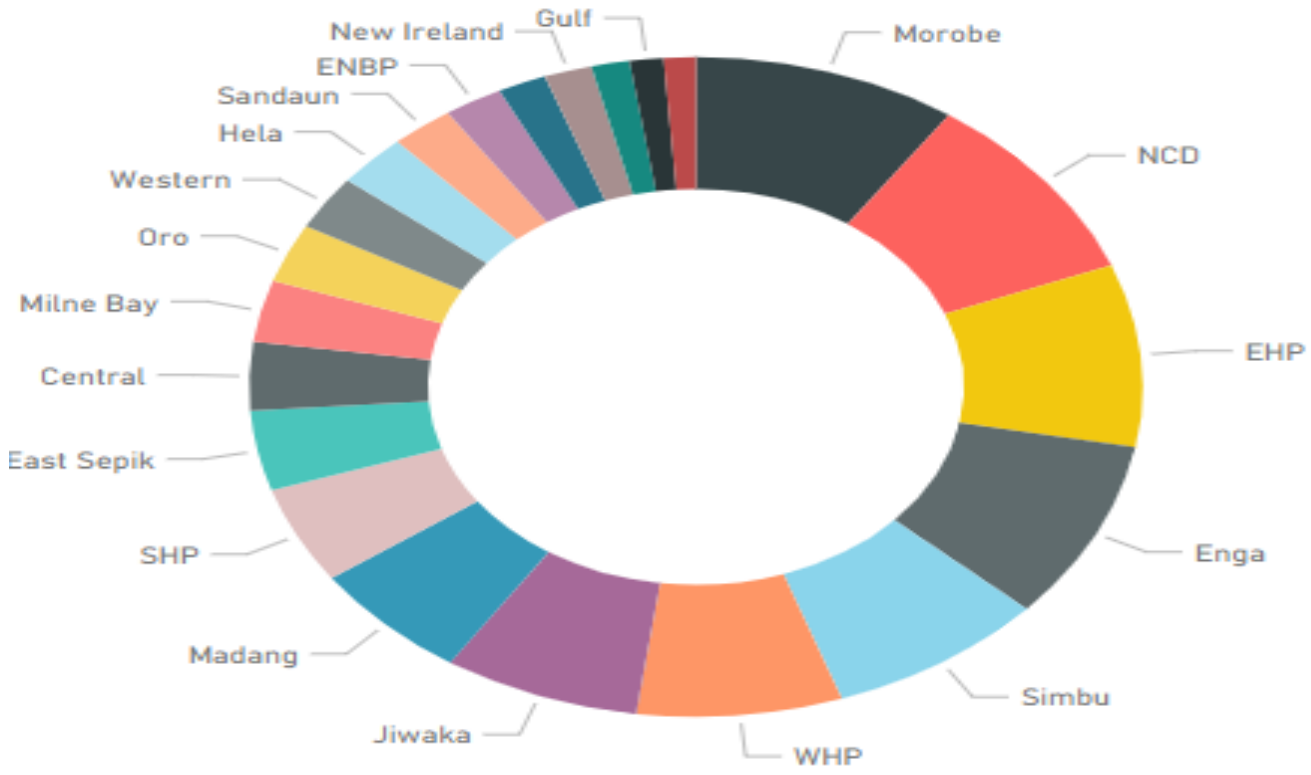
- 36.9 million living with HIV
- 1.7 million children (0-14) with HIV globally, only 54% (37-73) were receiving life saving ART in 2018 (unicef data).
- Globally children <15 years old,
  - 5%of people living with HIV,
  - 9% of new HIV infection and
  - 13% of all AID related deaths.
- Aim towards moving to achieving UNAIDS 90:90:90 Targets
  - 90% of people living with HIV knowing their HIV status
  - 90% of people who know their HIV positive status should access ART
  - 90% of people on Rx having supressed VL by 2020.

2018 National HIV Prevalence Provincial Distribution



Source: 2019 Spectrum estimates

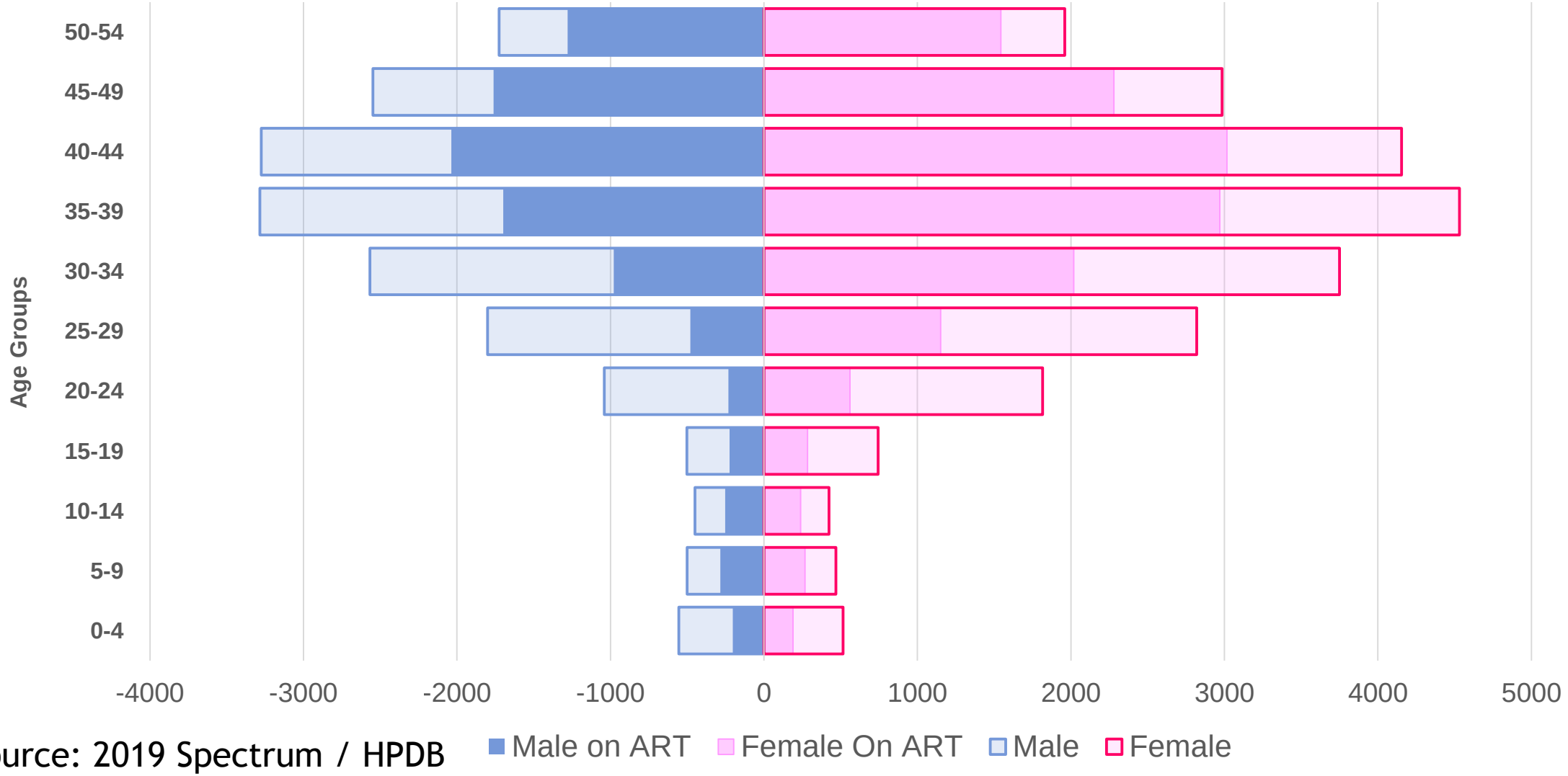
PLHIV Provincial Distribution



Province	# PLHIV
Morobe	4265
NCD	4182
EHP	3979
Enga	3925
Simbu	3545
WHP	3306
Jiwaka	3174
Madang	2626
SHP	2118
East Sepik	1738
Central	1488
Milne Bay	1349
Oro	1290
Western	1178
Hela	1153
Sandaun	1012
ENBP	947
WNBP	778
New Ireland	772
ARoB	615
Gulf	543
Manus	516

Source: 2019 Spectrum estimates

PLHIV Population Pyramid: 2018

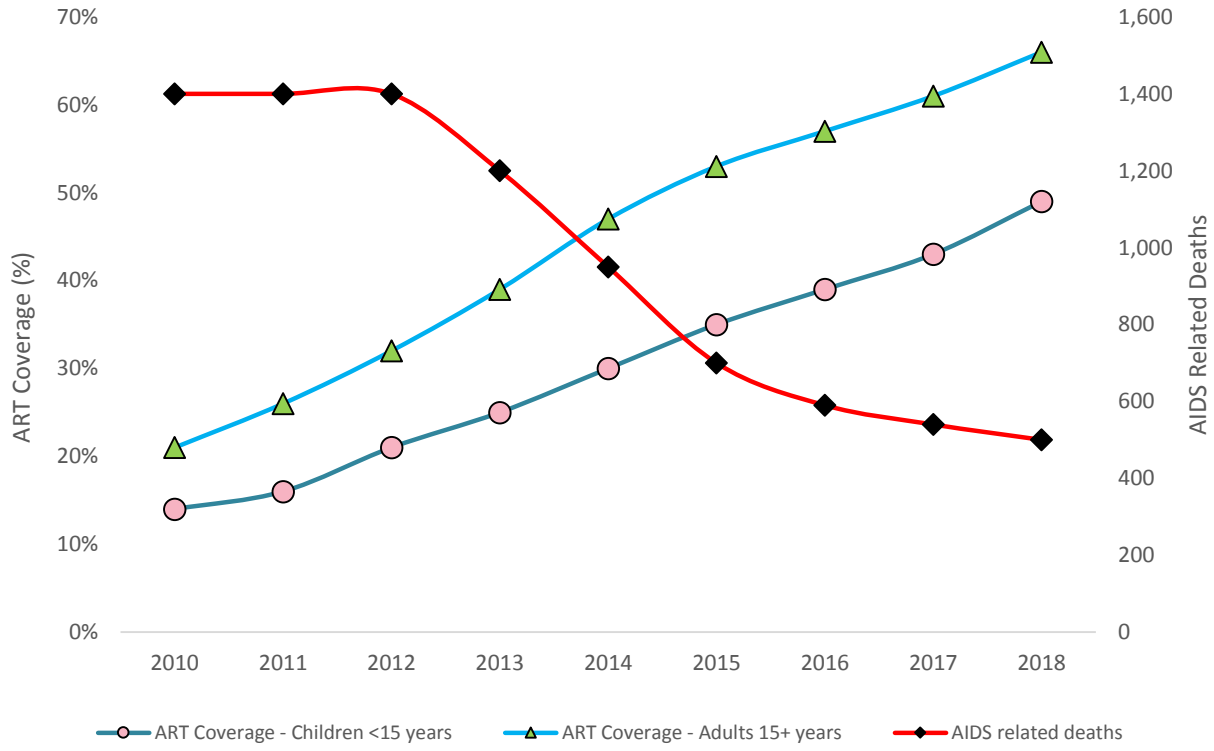


Source: 2019 Spectrum / HPDB

Papua New Guinea

- Children aged 0-14 living with HIV 2018 -2900 (2300-3500) (UNAIDS)
- Percentage of children living with HIV receiving ART 2018 – 49.2% (38.8- 58.1%) (Global AIDS Monitoring and UNAIDs 2019 estimates)
- Reported number of children receiving ART 2018 - 1400 (Global AIDS Monitoring)

ART coverage and AIDS-related deaths: 2010 - 2018

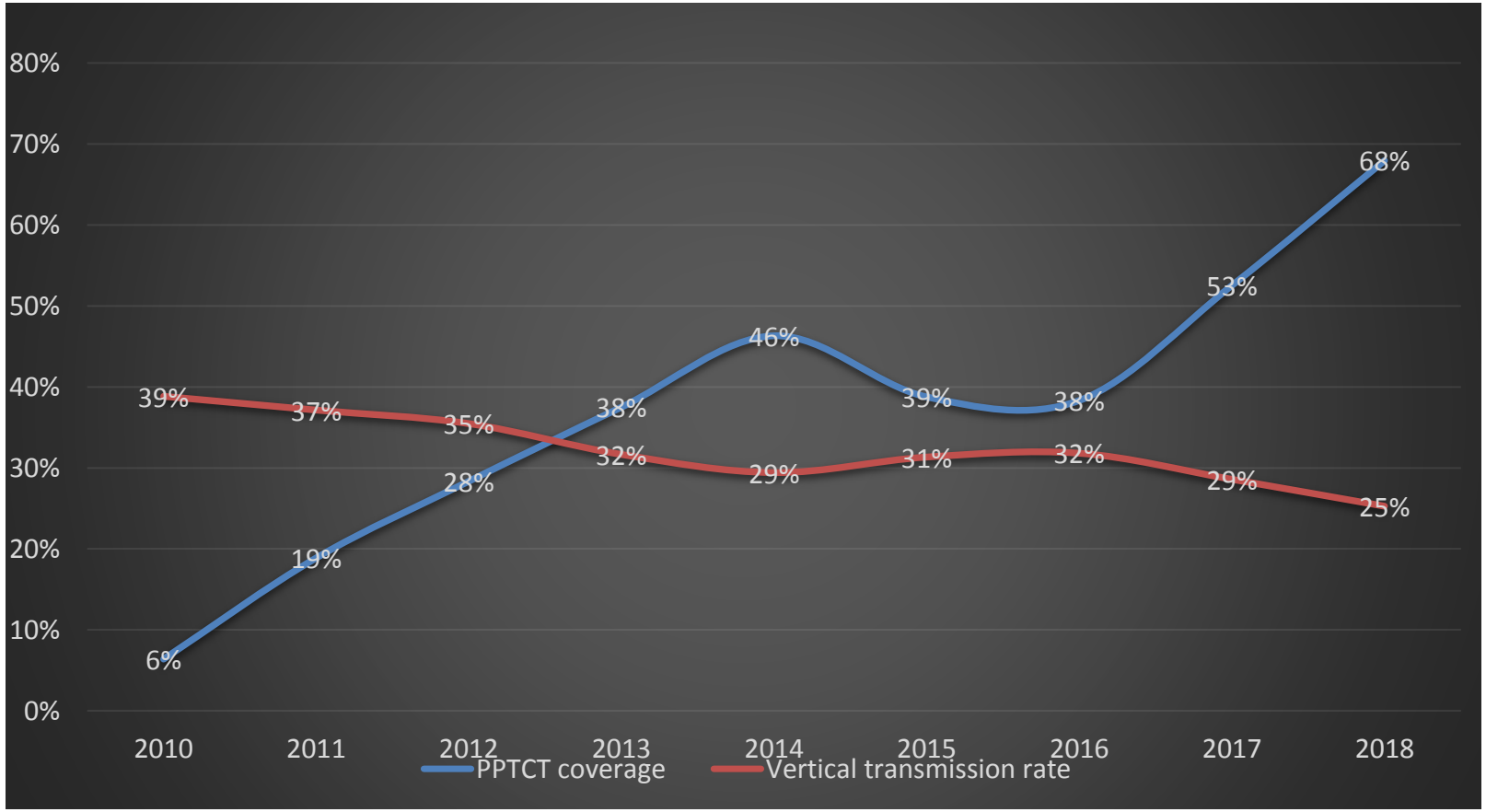


Source: 2019 Spectrum estimates

Early infant Diagnosis(EID) 2017 (CPHL data 2017)

	Number	Percentage
Total DBS received	953	
Positive	147	15%
Negative	806	85%
Number of Positive infants whose mothers on ART during pregnancy	50	34%
Number of Positive infant whose mothers were not on ART during pregnancy	97	66%

Prevention of Parent To Child Transmission Coverage



- Absence of intervention – vertical transmission 15-45%
- With effective intervention (periods of pregnancy delivery, labour and breastfeeding) - <5%
- What does this graph indicates?
  - (?)mothers are failing,
  - (?) resistance virus

Source: Situational analysis report - 2018

What’s New in the current guidelines?

- Test and treat Policy (introduced in the 2017 guidelines)
- New Antiretroviral guidelines
- Monitoring in children (Viral Load in children)

Test and Treat Policy

- ART should be initiated in all People (including children) living with HIV , regardless of WHO clinical staging or CD4 count.

ARV Prophylaxis for infants born to HIV positive mothers

- **Criteria for determining MTCT risk and prophylaxis regime for exposed**

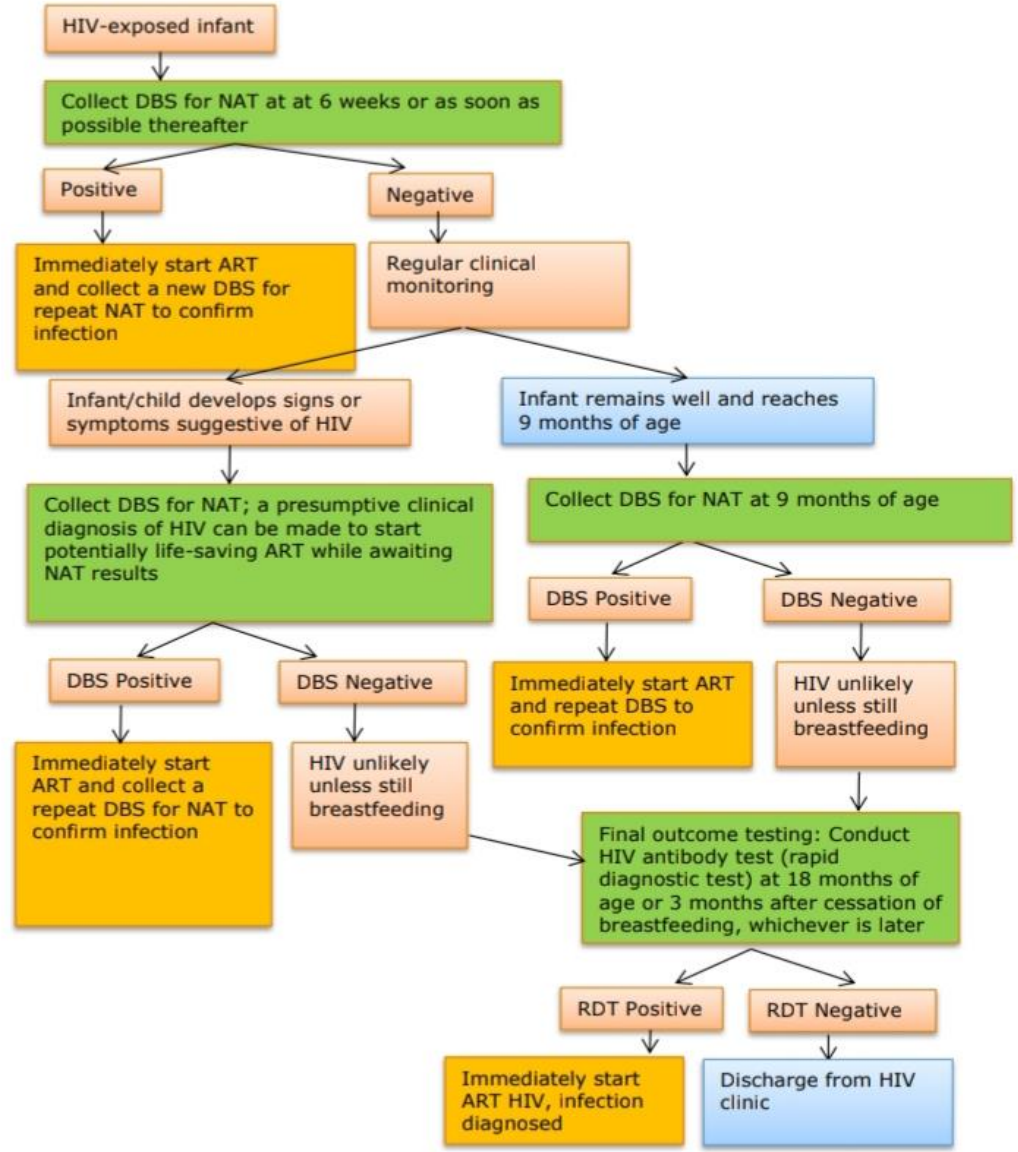
Women at High - risk of MTCT	**Women with low risk of MTCT**
• Has received <4 weeks of ART at the time of delivery or • Has Viral Load >1000 copies /ml in 4 weeks before delivery or • Diagnosed as HIV +ve during labour or breastfeeding period following a -ve prenatal HIV test result or • HIV +ve mother identified for the first times during post-partum period with or without –ve HIV test prenatally	• Has received at least 4 weeks of ART before delivery or • Has Viral Load of < 1000 copies /ml within 4 weeks prior to delivery
ARV prophylaxis for infants with a High risk of MTCT	**ARV prophylaxis for infants with a High risk of MTCT**
AZT and NVP for the first 6 weeks of life + **NVP only for an additional** 6 weeks **Total of 12 weeks**	**NVP only** for **6 weeks** of life **Total of 6 weeks**

Simplified infant prophylaxis dosing

Infant Age	NVP	AZT
Birth to 6 weeks		
Birth weight 2000 -2490g*	10mg once daily	10 mg twice daily
Birth weight >2500g	15mg once daily	15mg twice daily
> 6weeks to 12 weeks (for high risk MTCT)		
	20 mg once daily	
*For infants weighing less than 2 kg and older than 35weeks of GA the suggested dose are NVP 2mg/kg daily and AZT 4mg/kg twice daily		

Early Infant Diagnosis Algorithm

Figure 3. Testing strategy for HIV-exposed infants



Classes of ART

- Non nucleoside Reverse Transcriptase Inhibitors(NNRTI)
  - Nevirapine (NVP), Efaviranz(EFV)
- Nucleoside/nucleotide Reverse transcriptase Inhibitors(Ns/tRTI)
  - Tenofovir (TDF), Lamivudine(3TC), Abacavir (ABC), Zidovudine(AZT)
- Intergrase Inhibitors (INIs)
  - Dolutegravir (DTG), Raltegravir(RAL)
- Protease Inhibitors (PI)
  - Lopinavir/rotanovir (LPV/r)

Classes of ART Used

- Non nucleoside Reverse Transcriptase Inhibitors(NNRTI)
- Nucleoside/nucleotide Reverse transcriptase Inhibitors(Ns/tRTI)
- Protease Inhibitors (PI)
- Intergrase strand transfer Inhibitors (INSTI)
- Fusion Blockers(FB)

What class is New in the guideline?

- Integrase inhibitors (INIs)
  - Dolutegravir (DTG),
  - Raltegravir (RAL)

WHY??

Increase resistance in Non Nucleoside Reverse Transcriptase (NNRTI)Inhibitors world wide and Papua New Guinea in both the children and adult populations

Evidence – ART Resistance Patterns in children with HIV

J. Nuttal, V Pillay

- High levels of Pre-treatment Drug Resistance (PDR) – NNRTI
- Pre- Treatment drug resistance
  - Resistence in ARV Naïve induviduals initiating ART or induviduals with Prior ART Drug Exposure who are initiating or re initiaitng ART
- Resulted in Poor treatment outcome in infants and young children

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

PEDIATRIC INFECTIOUS DISEASES (I. BROOK, SECTION EDITOR)

Check for updates

Antiretroviral Resistance Patterns in Children with HIV Infection

J. Nuttall[1] · V. Pillay[1]

Published online: 28 February 2019

Abstract

Purpose of Review To provide an update on the patterns of HIV drug resistance in children, including pretreatment drug resistance (PDR) and acquired drug resistance (ADR), focusing on children in low- and middle-income countries (LMICs) for whom empiric first-line (FL) and second-line (SL) antiretroviral regimens are usually recommended.

Recent Findings High levels of PDR, particularly to non-nucleoside reverse transcriptase inhibitors (NNRTIs), and poor treatment outcomes on NNRTI-based FL antiretroviral therapy (ART) have been widely reported among infants and young children. There is a paucity of recent data on the use of protease inhibitor (PI)-based FL and SL regimens in children, but studies have reported poor tolerability, adherence problems and the development of PI resistance. Limited access to virological monitoring and HIV drug resistance testing contributes to delays in identifying treatment failure due to ADR and delays in switching to SL regimens in children.

Summary Implementation of FL ART regimens that have a higher barrier to developing resistance and are safe and well tolerated is required in order to attain global treatment targets. Although PI-based regimens may be effective as FL or SL treatment in children, lack of appropriate formulations leading to poor tolerability, drug-drug interactions, and cost considerations have negatively impacted their use among children in LMICs. There is hope that dolutegravir-based regimens recommended for children by the World Health Organization will be widely implemented once child-friendly formulations are available, and dosing and safety studies currently underway are completed, and that this will significantly improve treatment outcomes.

Keywords Antiretroviral · HIV · Resistance · Children

Systematic review (Jan 14 to Apr 17) on PDR

- 7 studies
- 1128 (HIV infected children) (age 0-114mnths)
  - Detectable drug resistance mutation 354 (31.3%)
  - Median Prevalence of NNRTI- 49.3% (7.5-100%)
- 4/7 studies >50% of PMTCT- exposed children has NNRTI DRM
- Similar finding in Uganda, south Africa

- WHO considers National PDR prevalence >10% to an ARV drug or drug class is an indication to transition to a different 1st line empiric First line ART treatment.

- The presence of PDR has been shown to be a strong predicator of treatment failure in FL ART in children

Extremely high prevalence of HIV pre-treatment drug resistance in Papua New Guinea – its health security, financial and policy implication (unpublished)

- *Introduction:* Determining the prevalence of Pre-treatment HIV drug resistance (PDR) is important to assess the effectiveness of FL regimes. A national representatives survey was conducted in PNG to determine the level of PDR

- *Methods:* A two stage cluster sampling method was employed to recruit the HIV treatment initiators with and without Prior exposure to ART in selected clinics. DBS were collected and tested for PDR

- *Results:* A total of 315 sequences were available for testing. The overall prevalence of PDR was 18.4%. The prevalence to NNRTI is 17.8% & NRTI 6.3%. The prevalence of PDR among people reinitiating ART was 42.2%.

- *Conclusion:* PNG has an extremely high prevalence of PDR especially to the FL treatment regime on reliant on NNRTI. The urgent removal of NNRTIs as part of the FL treatment is essential. A national strategy for addressing and halting PDR is a health security priority.

2017 OLD Guidelines

	Children < 3 years old	3-10 years old
Preferred Regime	ABC +3TC +LPV/r AZT + 3TC + LPV/r	ABC + 3TC + EFV
Alternate Regime	ABC +3TC +NVP AZT + 3TC + NVP	AZT +3TC + NVP or EFV ABC + 3TC + NVP TDF + 3TC + EFV or NVP
Special Circumstances	AZT + 3TC + ABC (only during TB treatment)	

Current Guidelines (2019)
Summary of ART for 1st line ART in neonates, infants and children

ART Regimes	Neonates	Children <20kg body weight	Children ≥20kg to less ≤30kg body weight
Preferred	ABC + 3TC + RAL	ABC + 3TC + LPV/r	ABC + 3TC + DTG
Alternate	ABC + 3TC + NVP	ABC + 3TC + RAL	ABC + 3TC + RAL ABC + 3TC + LPV/r
Special Circumstances (In case where no other alternatives are available)	ABC + 3TC + LPV/r	ABC + 3TC + EFV (<3yrs of age) AZT + 3TC + EFV(<3yrs of age AZT + 3TC + LPV/r AZT + 3TC + NVP AZT + 3TC + RAL	ABC + 3TC + EFV(<3yrs of age) AZT + 3TC + EFV(<3yrs of age) AZT + 3TC + LPV/r AZT + 3TC + NVP AZT + 3TC + RAL

Second line Treatment

	If patient failing first line ART regime below	⇨ Switch to second-line ART regime below
MEN/BOYS/WOMEN/GIRLS ≥30 kg Body Weight		
• Adults • Adolescents • Children Body weight more than 30 kg	TDF +3TC+DTG	AZT +3TC+LPV/r
	TDF +3TC+ EFV or NVP	AZT+3TC+DTG
	AZT+3TC+ EFV or NVP	TDF+3TC+DTG
BOYS/GIRLS ≥20kg to <30kg body weight		
BOYS/GIRLS ≥20kg to <30kg body weight	ABC + 3TC + DTG	AZT + 3TC + LPV/r
	ABC + 3TC + EFV or NVP	AZT + 3TC + DTG
	AZT + 3TC + EFV or NVP	ABC + 3TC + DTG

Second line Treatment cont…

	If patient failing first line ART regime below	Switch to second-line ART regime below
BOYS/GIRLS ≥20kg to <30kg body weight		
BOYS/GIRLS ≥20kg to <30kg body weight	AZT+3TC+LPV/r	ABC+3TC+ RAL
	ABC+3TC+LPV/r	AZT+3TC+ RAL
	ABC+3TC+EFV or NVP	AZT+3TC +LPV/r
	AZT+3TC+NVP	AZT+3TC +LPV/r

When to start ART?

ART should be commenced as soon as HIV diagnosis made, irrespective of CD4 count or clinical stage.

Early infant diagnosis and commencement of ART is key to optimising outcomes for children with perinatal HIV infection.

- Improves mortality
- Minimises HIV-associated immunodeficiency
  - Reduces opportunistic infections
- Better infant and early childhood growth and development
  - Optimises longer-term physical and neurocognitive development

When to start ART?

ART may be commenced in infants with a presumptive diagnosis of HIV, whilst awaiting confirmation (HIV PCR).

Presumptive infant diagnosis based on:

- HIV antibody positive, and
- Presence of an AIDS-defining illness

If TB/HIV diagnosed at same time

- TB treatment should begin at diagnosis, with ART to commence 2 weeks after starting TB therapy

When to change ART

Treatment failure

- Virologic failure
  - Viral load >1,000 copies/mL on two consecutive tests over 3 months, with adherence support following the first viral load test
- Immunologic failure (minimum 6 months ART)
  - Children <5 years: persistent CD4 <200 cells/mm^3
  - Children ≥5 years: persistent CD4 <100 cells/mm^3
  - Adolescents: persistent CD4 <100 cells/mm^3; or CD4 <250 cells/mm^3 after clinical failure
- Clinical failure (minimum 6 months ART)
  - New or recurrent WHO stage III/IV event

When to change ART

Toxicity

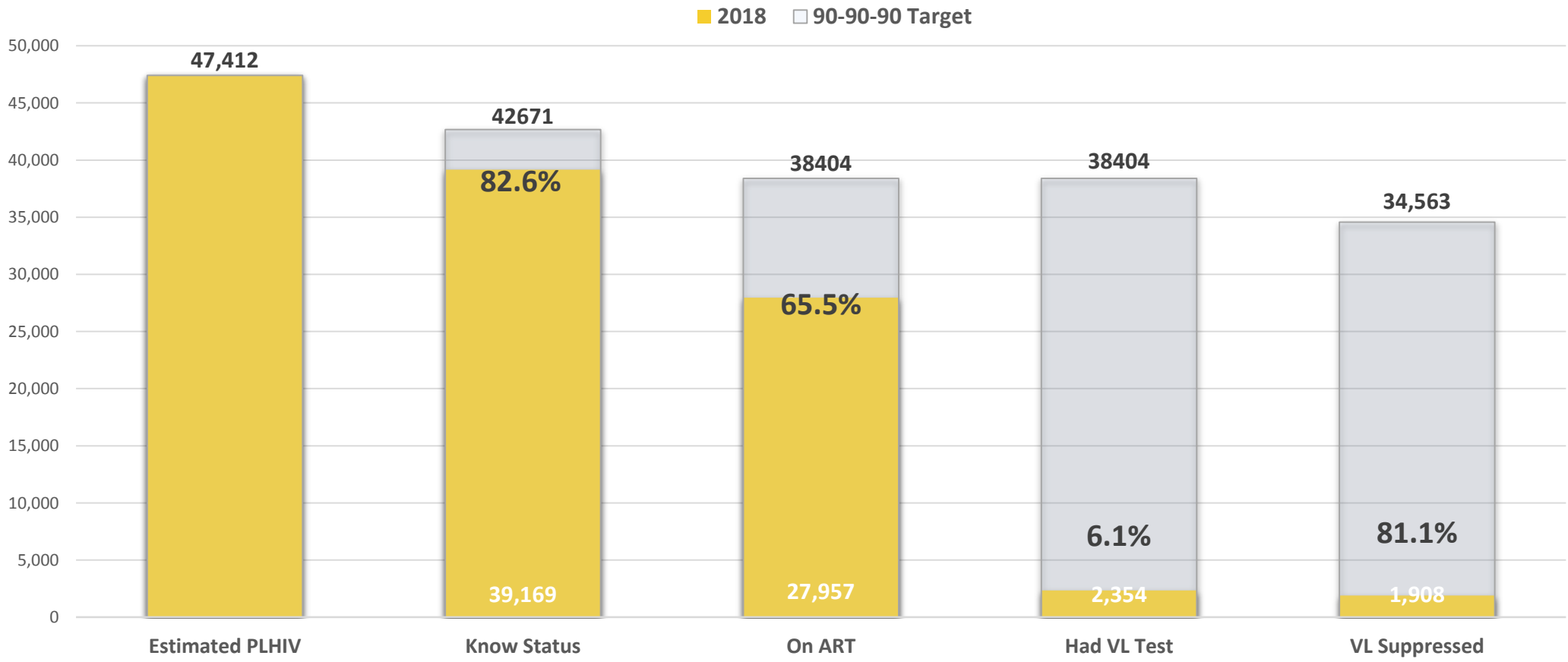
- Can substitute a single antiretroviral agent if toxicity due to one component of the combination ART regimen
- NRTIs can be switched for other NRTIs
  - ABC, AZT, TDF can be interchanged
- Switching the 3rd agent generally requires a change in drug class
  - Drug class switch between NNRTIs, PIs, INSTIs
  - Though NVP and EFV can be switched

Viral Load Algorithm

Figure 2. Viral Load Testing algorithm

*Evaluate patient for differentiated model of care (i.e. multi-month scripting)
**If patient is not responding after switch to second-line ART, refer the patient to medical officer for review.

2018 National HIV Care & Treatment Cascade



Sources: 2019 Spectrum Estimates; HPDB; VLSM;

Cotrimoxazole Preventative Therapy (CPT)

- Initiation of CPT
  - All patients are eligible for CPT as soon as they have a diagnosis of HIV
- Duration of CPT
  - CPT should not be discontinued, it should be continued throughout the persons lifetime.

Tuberculosis Preventative Treatment
Isoniazid prophylaxis treatment (IPT)

- Eligibility for IPT
  - All PLHIV who have no signs or symptoms suggestive of active TB are eligible for IPT
- Children living with HIV
  - >12 months or older should also receive IPT and
  - < 12 months should receive IPT if they have a known TB contact
- Duration of IPT
  - 6 months
  - INH mg/kg/day max of 300mg/day plus Vit. B12 or Pyridoxine(25mg/day) should be co-administrated

HIV TB Co- infection

Age /Weight	Children and infants initiating ART while on TB Rx	Children initiating TB Rx while on ART
Children 6 years or less (weight <20kg	• LPV/r – super boosting of Ritonavir 25mg (according to wt bands). After TB Rx back to normal regime. • Triple NRTI (AZT+3TC+ABC) for duration of TB Rx	• LPV/r based Regime – Ritonavir to increase (ratio 1:1 LPV/r) • NNRTI based regime (EFV more preferable than NVP) • Triple NRTI (AZT+3TC+ABC) for duration of TB Rx

HIV TB Co- infection

Age /Weight	Children and infants initiating ART while on TB Rx	Children initiating TB Rx while on ART
Children older than 6 years (≥20 kg or ≤30 kg	• 2NRTI + RAL (double dose of RAL - 12mg/kg BD) • No RAL use Triple NRTI (AZT +3TC + ABC) for duration of TB Rx. • DTG base Regime(ABC+3TC+DTG) – use triple NRTI(AZT+3TC+ABC) for the duration of TB Rx	• 2NRTI + RAL (double dose of RAL -12mg/kg BD) • No RAL use Triple NRTI (AZT +3TC + ABC) for duration of TB Rx. • DTG base Regime(ABC+3TC+DTG) – use triple NRTI (AZT+3TC+ABC) for the duration of TB Rx

Adherence - specific issues in children

- Palatability of formulations
- Limited once-daily and single-tablet regimens
- Dependence on caregivers
- Impact of issues within family unit
  - Poor physical or mental health of family member
  - Unstable housing
  - Poverty
  - Limited social support
  - Storage of medications
  - Confidentiality of medications

Discussion

- Low Pediatric ART coverage Rate (> 50% of children diagnosed with HIV are not on ART. WHY?)
- Adult ART Coverage 70%, ANC 68% (positivity rate of ANC mother 2%)
  - High Vertical Transmission rate ~25%
  - Compliance issues
  - adults or mother Defaulting /LTFU
- (?) Evidence of Drug Resistance in Mother (2017 –33% of mother on ART had positive infants)

Discussion

- Current evidence in PNG in adult population of extremely high prevalence rate of PDR of NNRIT 17% and prevalence PDR in those reinitiating ART 42%

  - (WHO Prevalence PDR>10%)
  - Indicates the need to change from NNRTI to DTG based Rx

Issues

- Delay Early infant Diagnosis – Longer turnaround time –delay diagnosis result in delay treatment (?- Gene Expert)

- High vertical transmission rate
  - Improve and strengthen ANC and treatment (All pregnant mother should be screen for HIV and started on ART ASAP).
  - Encourage all pregnant mothers to attend ANC

Issues

- Availability and sustainability of different Pediatrics Formulation
- Training or Up skilling of Pediatrician and other health care workers to provide comprehensive quality care to the Paediatric HIV or Paediatric HIV exposed Population in PNG.
- Adolescent Health
  - improve reproductive health education and awareness in school curriculum
  - Improve Counseling and Disclosure of Results
- De-centralizing Pediatrics HIV care) – One stop shop

Conclusion

- ART guidelines have changed NNRTI – DTG based ART)
- Funding – Big Issue /Paediatric Society
- Paediatrician/Registrars should show more interested in management and care of HIV patient.

Thank you


Having a NEGATIVE family
can be the most POSITIVE
thing in your life.
HIV +
HIV -
HIV -
HIV -