

# Pediatric HAART 3: Characteristics of antiretroviral drugs

Unit 10.1

Paediatric Antiretroviral Therapy Workshop  
Institute for Human Virology-Nigeria ACTION

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# Goals



- Describe the important characteristics of any antiretroviral drug
- Be familiar with the major characteristics of HIV drugs likely to be used in children in PEPFAR programs

# Antiretroviral drug characteristics 1



- **Name: Generic, brand, and abbreviation**
- **Formulations.**
  - Liquids: taste issue; large volume; must be measured accurately; suspensions may settle
  - Tabs convenient, can be crushed, a little harder to swallow than capsules
  - Capsules: Humidity a problem; some can be opened (EFV), others contain liquid (LPV/r)
- **Dosage**
  - Never exceed adult dosage
  - Weight-based: Easy to calculate
  - Body surface area based: More accurate for some drugs

$$SA = \sqrt{\frac{\text{Height(cm)} \times \text{Weight(kg)}}{3600}}$$

## Antiretroviral drug characteristics 2

- **Virology**
  - Potency: How active is drug against wild-type virus?
  - Resistance barrier: How many mutations are needed for resistance?
- **Metabolism and elimination**
  - Renal versus hepatic (or both)
- **Drug interactions**
  - Pharmacokinetic: Effects on absorption and metabolism
  - Pharmacodynamic and virologic: Effect on antiretroviral activity
  - Additive or synergistic toxicity

- **Side effects and toxicity**
  - What is time course?
  - How common?
  - How serious?
  - Is it reversible?
  - How to monitor?
  - How managed?

# Antiretroviral drugs 2006



## Nucleoside analogues

- Zidovudine
- Stavudine
- Lamivudine
- Didanosine
- Abacavir
- Emtricitabine
- Tenofovir

## Non-nucleoside RT inhibitors

- Nevirapine
- Efavirenz
- Delavirdine

## Fusion inhibitor

- Enfuvirtide (T-20)

## Protease inhibitors

- Nelfinavir
- Indinavir
- Saquinavir
- Amprenavir
- Ritonavir
- Lopinavir/ritonavir
- Atazanavir
- Fosamprenavir
- Tipranavir
- Darunavir

## PEPFAR drugs for:

**Children- Yellow**

Adults & selected  
children- Blue

# Stavudine



<b>Brand/Abbr.</b>	<b>Zerit, D4T</b>
<b>Class</b>	<b>Nucleoside (thymidine) analogue</b>
<b>Formulations &amp; palatability</b>	<b>Syrup: 1 mg/ml (taste: fair) Capsules: 15, 20, 30, 40 mg (small)</b>
<b>Storage</b>	<b>Syrup: 4 C X 30 days. Caps: 15-30 C</b>
<b>Dosage</b>	<b>Child: 1 mg/kg up to 30 mg Adult: 30-60 kg: 30 mg &gt;60 kg: 40 mg</b>
<b>Elimination</b>	<b>Renal</b>

# Stavudine 2

<b>Interactions</b>	<b>Zidovudine inhibits D4T activation- do not use together.</b> <b>Increased toxicity with DDI</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Initial tolerability: very good</b> <b>Toxicity: moderate- lactic acidosis, lipoatrophy, hyperlipidemia, insulin resistance, hepatic, pancreatitis, neuropathy (mostly adults)</b>
<b>Potency</b>	<b>Moderate</b>
<b>Genetic barrier to resistance</b>	<b>Moderate; hypersensitivity with M184V</b>

# Lamivudine

<b>Brand/Abbr.</b>	<b>Epivir, 3TC</b>
<b>Class</b>	<b>Nucleoside (cytosine) analogue</b>
<b>Formulations &amp; palatability</b>	<b>Syrup: 10 mg/ml (taste: great) Tabs: 150 mg (small)</b>
<b>Storage</b>	<b>Syrup &amp; tab: Stable at RT</b>
<b>Dosage</b>	<b>Child: 4 mg/kg b.i.d. Adult: 150 mg b.i.d.</b>
<b>Elimination</b>	<b>Renal</b>

# Lamivudine-2



<b>Interactions</b>	<b>None</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Very well tolerated Possible rebound hepatitis B when stopped Lactic acidosis?, hepatic ?</b>
<b>Potency</b>	<b>Moderate</b>
<b>Genetic barrier to resistance</b>	<b>Low: M184V mutation is readily selected and confers high level resistance BUT also causes increased sensitivity to ZDV, D4T, and TDF and decreases viral fitness</b>

# Zidovudine

<b>Brand/Abbr.</b>	<b>Retrovir, ZDV, AZT</b>
<b>Class</b>	<b>Nucleoside (thymidine) analogue</b>
<b>Formulations &amp; palatability</b>	<b>Syrup: 10 mg/ml (taste: fair) Caps: 100 mg (small) Tab: 300 mg (medium)</b>
<b>Storage</b>	<b>15-25 C</b>
<b>Dosage</b>	<b>Child: 160 mg/m<sup>2</sup> t.i.d.; ? 240 mg/m<sup>2</sup> b.i.d. (not tested but commonly used in older children) Adult: 300 mg b.i.d.</b>
<b>Elimination</b>	<b>Hepatic glucuronidation and elimination of glucuronide in urine</b>

# Zidovudine-2



<b>Interactions</b>	<b>Zidovudine inhibits D4T activation- do not use together. Rifampin reduces exposure by half</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Generally well tolerated in children. Common: anemia, neutropenia, mild GI intolerance, fatigue, headache, dark fingernails. Uncommon: myopathy, cardiomyopathy, hepatitis, lactic acidosis.</b>
<b>Potency</b>	<b>Moderate</b>
<b>Genetic barrier to resistance</b>	<b>Moderately high Hypersensitive to M184V virus</b>

# Didanosine



<b>Brand/Abbr.</b>	<b>Videx DDI</b>
<b>Class</b>	<b>Nucleoside (adenosine) analogue</b>
<b>Formulations &amp; palatability</b>	<b>Suspension in antacid: 10 mg/ml (tastes like antacid- chalky) Chewable/dissolvable tabs: 50, 100, 200 mg (must take at least 2 tabs)</b>
<b>Storage</b>	<b>Suspension: 4 C X 30 days Tabs: Room temp</b>
<b>Dosage</b>	<b>Child: 120 mg/m<sup>2</sup> b.i.d. Adult: &gt; 60 kg 200 mg b.i.d. Must take on empty stomach</b>
<b>Elimination</b>	<b>Extensive metabolism</b>

# Didanosine-2



<b>Interactions</b>	<b>Buffer incompatible with food, tetracyclines, fluoroquinolones, ketoconazole, itraconazole, IDV, RTV, ATV, NFV, LPV/r, TDF. DDI levels increased by TDF. Can dose with ZDV, D4T, EFV, NVP</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Generally well tolerated in children. Common: pancreatitis, neuropathy (mainly adults) Uncommon: Lactic acidosis, GI upset, hepatic toxicity</b>
<b>Potency</b>	<b>Moderate</b>
<b>Genetic barrier to resistance</b>	<b>Moderate</b>

# Abacavir

<b>Brand/Abbr.</b>	Ziagen, ABC
<b>Class</b>	Nucleoside (guanosine) analogue
<b>Formulations &amp; palatability</b>	Syrup: 20 mg/ml (taste: fair) Tabs: 300 mg
<b>Storage</b>	Room temp
<b>Dosage</b>	Child: 8 mg/kg b.i.d. Adult: 300 mg b.i.d.
<b>Elimination</b>	Dehydrogenation, glucuronidation; metabolites in urine. No adjustment for renal failure

# Abacavir-2



<b>Interactions</b>	<b>Inducers of glucuronidation might lower levels</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Generally well tolerated. Mild nausea. Hypersensitivity reaction: Onset few days-6 weeks after starting drug- fever, rash, malaise or hypotension, GI upset, respiratory. Progresses with continued dosing. Can be fatal. Severe reaction if rechallenged.</b>
<b>Potency</b>	<b>Moderate-high (most potent NRTI)</b>
<b>Genetic barrier to resistance</b>	<b>Moderate</b>

# Tenofovir

<b>Brand/Abbr.</b>	<b>Viread, TDF</b>
<b>Class</b>	<b>Nucleotide analogue</b>
<b>Formulations &amp; palatability</b>	<b>Tab: 300 mg Truvada: 300 mg TDF/200 mg FTC</b>
<b>Storage</b>	<b>Room temp</b>
<b>Dosage</b>	<b>Adult: 300 mg OD</b>
<b>Elimination</b>	<b>Renal</b>

# Tenofovir-2



<b>Interactions</b>	<b>Minimal</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Very well tolerated</b> <b>Renal toxicity (uncommon)</b> <b>? ?Bone mineral loss in children: 2 small studies with different results</b>
<b>Potency</b>	<b>Moderate</b>
<b>Genetic barrier to resistance</b>	<b>Moderate</b>

# Nevirapine



<b>Brand/Abbr.</b>	<b>Viramune, NVP</b>
<b>Class</b>	<b>Non-nucleoside reverse transcriptase inhibitor</b>
<b>Formulations &amp; palatability</b>	<b>Suspension: 10 mg/ml (bitter) Tabs: 200 mg (scored)</b>
<b>Storage</b>	<b>Room temperature</b>
<b>Dosage</b>	<b>NVP must be given q.d. for first 2 weeks because of autoinduction of metabolism and to reduce risk of hypersensitivity. Child: 120 mg/m<sup>2</sup> b.i.d. (&lt; 4 y.o. 200 mg/m<sup>2</sup> b.i.d.; 4-8 y.o. 150 mg/m<sup>2</sup> b.i.d., &gt;8 y.o. 120 mg/m<sup>2</sup> b.i.d.) Adult: 200 mg b.i.d.</b>

# Nevirapine-2



<b>Elimination</b>	<b>Hepatic P450 metabolism</b>
<b>Interactions</b>	<b>Rifampin lowers NVP by 1/3- use EFV NVP lowers ketoconazole by 2/3 NVP lowers LPV level- increase LPV dosage</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Common: Rash. If mild, check LFTs, continue dosing. If signs of Stevens-Johnson, stop drug. Hepatitis- can be severe, especially with higher CD4 and in women. Monitor LFTs in adults. Risk in children not as well described.</b>
<b>Potency</b>	<b>High</b>
<b>Genetic barrier to resistance</b>	<b>Very low- resistance can develop after single dosage given without other ARVs</b>

# Efavirenz

<b>Brand/Abbr.</b>	<b>Sustiva, Stocrin, EFV</b>
<b>Class</b>	<b>Non-nucleoside reverse transcriptase inhibitor</b>
<b>Formulations &amp; palatability</b>	<b>Capsules: 50, 100, 200 mg Caps are easily opened, powder does not dissolve but is tasteless</b>
<b>Storage</b>	<b>Room temp</b>
<b>Dosage</b>	<b>Child: &gt;3 years old: 15 mg/kg q.d. Adult: 600 mg q.d.</b>
<b>Elimination</b>	<b>Hepatic P450 metabolism</b>

# Efavirenz-2

<b>Interactions</b>	<b>Decreases levels of LPV/r (increase dosage), unboosted PIs, other drugs</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Common: Transient CNS effects (sleepiness, strange dreams) usually resolve after week-month. Rash- if mild, continue dosing; if signs of Stevens-Johnson, stop drug. Uncommon: Increased transaminases Possible birth defects?</b>
<b>Potency</b>	<b>Very high</b>
<b>Genetic barrier to resistance</b>	<b>Very low.</b>

# Nelfinavir



<b>Brand/Abbr.</b>	<b>Viracept NFV</b>
<b>Class</b>	<b>Protease inhibitor</b>
<b>Formulations &amp; palatability</b>	<b>Powder: 50 mg/1.25 ml scoop (mix in milk or water- makes sandy moderately bitter-sweet slurry) Tabs: 250 mg (Can be crushed or dispersed; mildly bitter)</b>
<b>Storage</b>	<b>RT</b>
<b>Dosage</b>	<b>Must take with meal or milk Child: &lt;1 year 40-50 mg/kg t.i.d. &gt;2 year 45-55 mg/kg b.i.d. Adult: 1250 mg b.i.d.</b>

# Nelfinavir-2



<b>Elimination</b>	<b>Hepatic P450 metabolism; metabolite M8 is active</b>
<b>Interactions</b>	<b>Mild P450 inducer and inhibitor</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Diarrhea is common, otherwise well-tolerated. Class effects including cholesterol increases; insulin resistance</b>
<b>Potency</b>	<b>High</b>
<b>Genetic barrier to resistance</b>	<b>Low-Moderate</b>

# Lopinavir/ritonavir

<b>Brand/Abbr.</b>	<b>Kaletra, LPV/r</b>
<b>Class</b>	<b>Protease inhibitor</b>
<b>Formulations &amp; palatability</b>	<p><b>Solution: 80 mg/ml LPV + 20 mg/ml RTV (extremely bitter)</b></p> <p><b>Caps: 133 mg LPV/33 mg RTV</b></p>
<b>Storage</b>	<b>4 C. Stable 25 C X 2 months. Keep caps from moisture</b>
<b>Dosage</b>	<p><b>Take with food</b></p> <p><b>Child &gt; 6 months: 230 mg/m<sup>2</sup> LPV b.i.d.</b></p> <p><b>Adult: 400 mg LPV b.i.d.</b></p> <p><b>Increase dosage by 1/3 if NVP or EFV used</b></p>

# Lopinavir/ritonavir-2



<b>Elimination</b>	<b>Hepatic P450 metabolism</b>
<b>Interactions</b>	<b>Very potent inhibitor of P450 enzymes- profound effect on elimination of multiple drugs. Rifampin lowers LPV to ¼. Increase dosage 1/3 with NVP or EFV.</b>
<b>Tolerability, side effects &amp; toxicity</b>	<b>Common: Nausea and vomiting &gt; diarrhea; taste perversion. Class effects including cholesterol increases; insulin resistance</b>
<b>Potency</b>	<b>Extremely high- the most potent ARV</b>
<b>Genetic barrier to resistance</b>	<b>Extremely high. Resistance does not develop when used as first PI. Resistance only after other PIs have failed and requires 5-10 mutations.</b>

# Major early or acute-onset ARV toxicities by syndrome



- Anemia, neutropenia: ZDV
- Rash: NVP, EFV, ABC
- Systemic hypersensitivity: NVP, ABC
- Nausea, vomiting: LPV/r >> others
- Diarrhea: NFV > LPV/r
- CNS disturbances: EFV
- Neuropathy: DDI > D4T
- Pancreatitis: DDI >> D4T, ? LPV/r
- Hepatitis: NVP > others
- Myopathy: ZDV
- Lactic acidosis- acute severe (very rare in children):  
DDI, D4T, ZDV, 3TC

# Major chronic ARV toxicities by syndrome



- Lipodystrophy: D4T > DDI, ZDV, ? PIs
- Hypercholesterolemia: D4T, NFV, LPV/r
- Hypertriglyceridemia (rare in children): LPV/r, NFV
- Insulin resistance: D4T, LPV/r, NFV
- Bone disease: ??