

Pediatric ART 5:

Drug metabolism and interactions
Antiretroviral toxicity
Immune reconstitution syndromes
HIV/TB co-infection

Unit 12.1

Paediatric Antiretroviral Therapy Workshop
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*The person who takes medicine must recover
twice, once from the disease and once from
the medicine.*

William Osler

Goals

- Describe the major pathways for antiretroviral drug metabolism and how this leads to drug interactions
- Describe the basis for the major toxicities of each ARV drug class
- Identify the major immune reconstitution syndromes
- Recognize the interactions between antiretroviral and anti-TB drugs

Children in all shapes and sizes: how much drug to give?

- Weight-based dosing: simple, but correct dosage correlates better with body surface area (BSA) for some drugs
- New WHO paediatric ARV drug table gives dosages according to weight, but for some drugs, dosage has been calculated by surface area, then listed according to weight.
- Formula for BSA (m²)
$$SA = \sqrt{\frac{\text{Height(cm)} \times \text{Weight(kg)}}{3600}}$$
- Nomogram for BSA: included in printed and CD material

Drug dosage in children with wasting: are we underdosing?

- No data on ARV drug dosing in children with wasting
- Weight may underestimate size of organs that metabolize or eliminate drug
- Should we use ideal body weight to calculate drug dosages?

Activation of nucleoside analogues

- All NRTIs are given as *prodrugs*
 - Drug must be triphosphorylated intracellularly to active drug
 - Prodrug has short half-life in plasma, but activated drug has long half-life intracellularly
 - Level of NRTI in blood is not good measure of its activity
- ZDV inhibits triphosphorylation of D4T:
never use together

Antiretroviral elimination

- Renal excretion unchanged: D4T, 3TC
- Glucuronidation in liver, then excretion of glucuronide in urine: ZDV, ABC
- Other metabolism: ABC, DDI
- Hepatic P450 cytochrome systems: All NNRTIs and protease inhibitors
- Each of these mechanisms may develop at different rates in the child

Inducers of glucuronidation

- Drugs affected: ZDV > ABC
- Poorly studied!
- Rifampin lowers ZDV exposure to 47%
- No data for ABC
- Other potent inducers of glucuronidation include phenobarbital, phenytoin (Dilantin), carbamezipine (Tegretol)

Hepatic P450 cytochrome system (CYP)

- Multiple enzymes
- Genetic variation
- A particular drug may
 - Be metabolized by one or more CYP
 - Inhibit one or more CYP (immediate effect)
 - Induce activity of one or more CYP (delayed effect- takes 1-2 weeks for full induction)
 - Do all the above!

Development of CYP system

- Very slow in newborn: 1 dose of NVP lasts a week
- CYP then becomes very active in infants-
difficult to get adequate drug levels in
infants and young children

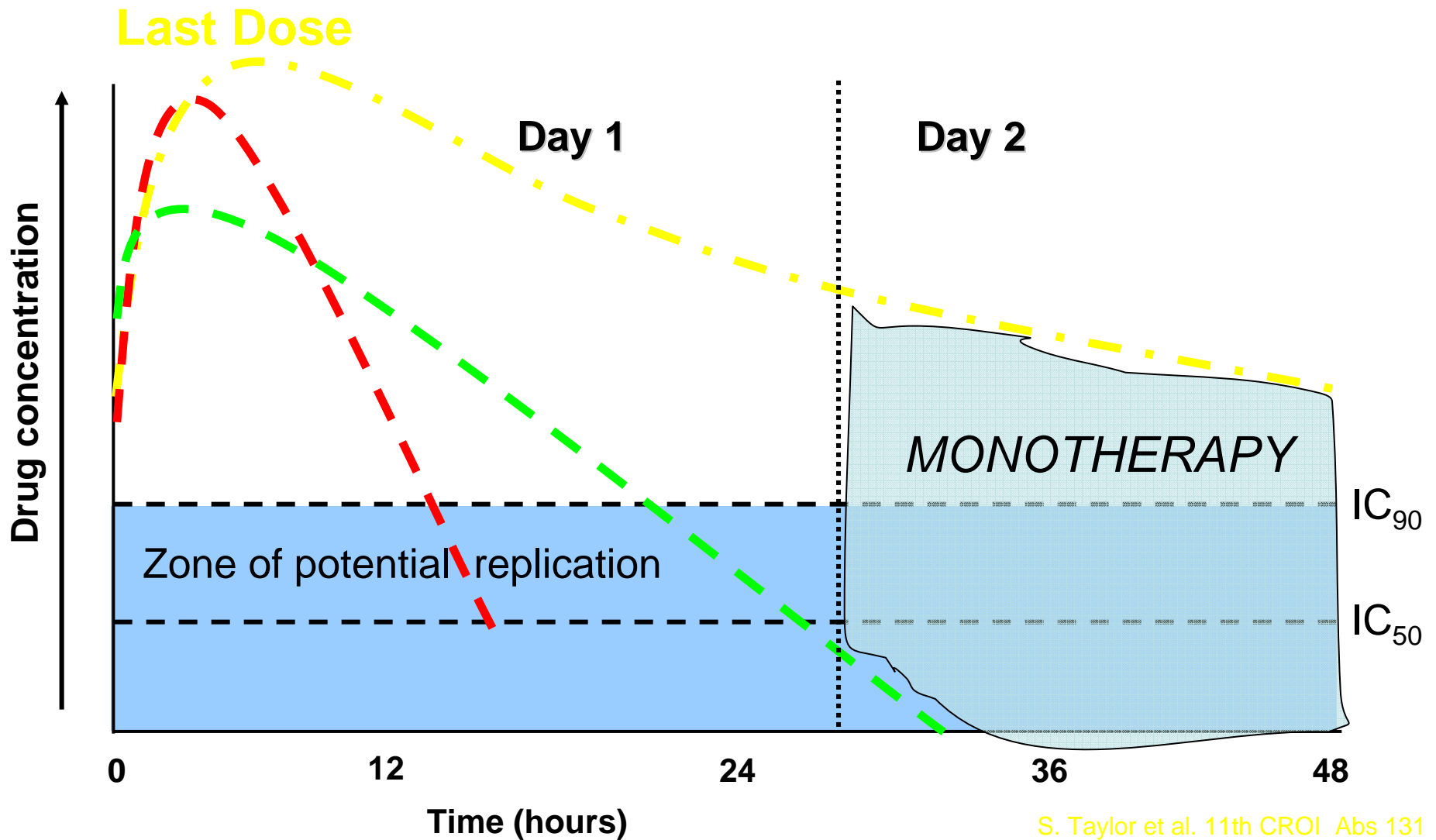
Autoinduction of nevirapine metabolism

- Clearance of NVP more than doubles after 2 weeks in young children
- High levels of NVP associated with allergic or hepatic reactions
- Start NVP with one daily dose for two weeks, then give twice daily
- Younger children require relatively higher dosages of NVP or EFV- new WHO drug table has taken this into account

NNRTI half-life and the NNRTI “tail”

- NNRTIs have long half-life: NVP about 24 hours and EFV about 40 hours
- NNRTIs have very low resistance barrier: single mutation gives high-level resistance
- When HAART is stopped, NNRTI may take days to be eliminated. Other ARVs are gone, but NNRTI persists. NNRTI-resistant virus may emerge.
- If possible stop NNRTI 1 week before stopping other ARVs when treatment must be stopped.
- Also an issue for NVP PMTCT regimens

Stopping drugs with different half lives



CYP inducers and ARVs

- NVP, EFV, rifampin, induce protease inhibitor metabolism, lowering PI levels
- Effect of NVP and EFV on NFV is negligible
- LPV significantly lowered
 - LPV dosage without NVP or EFV: 230 mg/m² b.i.d.
 - LPV dosage with NVP or EFV: 300 mg/m² b.i.d.
- Other affected drugs: Other PIs, ketoconazole, statins, ethynil estradiol (variable), probably many others

CYP inhibition: a blessing and a curse

- Inhibition of CYP3A4 >> other CYP:
RTV > IDV, NFV, ATV, DLV > SQV
- Both inhibition and induction: EFV, APV
- RTV is extremely potent inhibitor of CYP3A4
 - Co-administered drug may have very slow clearance
 - Single dose of co-administered drug will not reach high levels, but will persist
 - Danger of accumulated drug with repeated dosing

Drugs affected by RTV

- HIV protease inhibitors: LPV, SQV, IDV, NFV, ATV, APV
- Antibiotics: Rifabutin, ketoconazole, clarithromycin (~1.8-fold increase), azithromycin, itraconazole
- Statins, benzodiazepines, Viagra, Ca²⁺ channel blockers, cisapride, tricyclic antidepressants

Use of RTV as a pharmacoenhancer (“Boosted” protease inhibitors)

- RTV inhibition of CYP3A allows for decreased dosage, increased dosing interval, and increased drug levels of several PIs
- Exposure (AUC) increased:
 - SQV 20-60 fold
 - LPV >100 fold
 - IDV 4-5 fold
 - ATV 3.4 fold
- Basis for LPV/r coformulation (Kaletra)
- RTV dosage in boosted regimens is low- no virologic effect

Antiretroviral toxicities

- **Class effects:** toxicities shared by members of a class *to a variable degree*
- **Unique effects:** toxicities unique to a drug
- **Hypersensitivity reactions:** idiosyncratic- some people get it, most don't
- **Disease-related:** Many "side effects" are actually manifestations of HIV. Effects of disease and side effects of drug may overlap.
 - E.g. HIV and ZDV both cause anaemia
 - Sometimes anaemia can *improve* with ZDV due to control of HIV infection

Toxicity of antiretrovirals

Nucleosides

Mitochondrial toxicity

neuropathy
myopathy
pancreatitis
myelotoxicity
hepatitis
lactic acidosis
lipoatrophy
...

Non-nucleosides

Hypersensitivity

exanthema
fever
mucosae
multiorgan failure
...

PIs

Metabolic abnormalities

hyperlipidemia
insulin resistance
diabetes
↑visceral fat
...

Mechanism of NRTI toxicity

- NRTIs block HIV cDNA chains
- NRTIs also incorporated into mitochondrial DNA- mitochondria can't replicate
- What are mitochondria?
 - Organelles in cytoplasm of all cells
 - The energy factory of cells: oxidative phosphorylation
 - Contain their own chromosome with separate system for DNA replication, transcription, translation

NRTI toxicity

- Approximate order of mitochondrial toxicity:
D4T > DDI, ZDV > 3TC > ABC, TDF
- Lactic acidosis
 - Rare in adults, *extremely rare* in children
 - Body can't utilize oxygen, becomes acidotic
 - Symptoms: Weakness, abdominal upset
 - 50% mortality
- Lipoatrophy: loss of subcutaneous fat (but not visceral fat in abdomen, breasts, upper back):
D4T; ?other NRTIs

NRTI toxicity (2)

- Pancreatitis: DDI > D4T
- Neuropathy: D4T , DDI
- Hepatitis: ZDV, D4T, DDI, 3TC, ?ABC
- Hepatic steatosis, hepatitis, death: D4T + DDI combined in pregnant women
- Hyperlipidemia & insulin resistance: D4T
- Myopathy: ZDV
- Anemia, neutropenia: ZDV (MCV always increases)
- ?Bone mineral loss: TDF

Fetal toxicity of ARVs

- No clear association with birth defects
- Mild (?? benign) lactic acidosis in infancy: DDI > ZDV, 3TC, D4T
- ZDV: mild anaemia in newborn
- EFV: ? Teratogenic
 - Birth defects in 3/20 monkeys conceived in mothers given EFV
 - Case reports in humans but prospective series has not found increase in birth defects

Potential fetal/neonatal toxicity of ZDV/3TC

- ZDV + 3TC from early 2nd trimester ***through*** 6 weeks of age: degenerative brain disease.
- ZDV + 3TC used commonly in pregnant women
 - NOT associated with brain disease if 3TC stopped at birth
 - NOT seen in infants given ZDV + 3TC for treatment (whose mothers generally did not take ARVs)

Abacavir hypersensitivity syndrome

- About 5-7% of European-Americans, 3% of African-Americans
- Onset within 6 weeks of at least 3:
 - **Fever**
 - Rash
 - GI: emesis, abdominal pain, diarrhea
 - Weakness, hypotension
 - \pm Cough, respiratory failure
- Worse with each dose
- Resolves if drug stopped promptly
- Fulminant reaction if rechallenged
- ABC is a great drug: try to establish diagnosis

Nevirapine hypersensitivity

- Mild rash is common, resolves with continued dosing or discontinuation and rechallenge
- Stevens Johnson: Darkening or blistering, mucosal involvement, arthritis, fever-
discontinue drug
- Hepatitis
 - Usually in first 6 weeks
 - Women with CD4 > 250: 11%
 - Men with CD4 > 400: 6.3%
 - ? Children (14% have AST > 250)
 - May be associated with rash

Efavirenz toxicity

- Benign rash (similar to NVP)
- Stevens-Johnson (rare)
- CNS side effects
 - With first dose but usually resolves in 1-4 weeks
 - Very common; worse in slow metabolizers (20% of African-Americans)
 - Sleepiness, bizarre dreams, feeling strange
 - May exacerbate depression
- Birth defects??
- Mild total and HDL cholesterol elevation
- Mild increase transaminases

Protease inhibitor toxicity (except ATV)

- Hypercholesterolemia: elevation always seen
- Hypertriglyceridemia
 - Worse in adults
 - Can cause pancreatitis
- Insulin resistance
 - Type 2 diabetes in adults
- Increased visceral fat (upper back, breasts, intra-abdominal)

GI side effects of protease inhibitors

- **NFV**: Little nausea or vomiting but **diarrhea** common
- **LPV/r**, other RTV-boosted PIs: **Nausea and vomiting** common
 - Improves over time
 - Less if taken with food
 - \pm diarrhea
- **LPV/r taste is terrible**- may vomit trying to swallow

HIV and TB

- TB endemic in areas of high HIV prevalence
- TB is an opportunistic infection in HIV
- Always look for TB in HIV patient and for HIV in TB patient
- PPD insensitive for diagnosis (>5 mm is positive)
- HAART can cause immune reconstitution syndrome in TB patient

Antituberculous and antiretroviral medications: a major challenge

- TB & HIV drugs may interact (especially rifampin)
- Combined toxicity of TB & HIV drugs (e.g. rifampin + SQV)
- Challenge of adhering to two multidrug regimens

Immune reconstitution syndromes

- Relieved of immunosuppression of HIV infection, immune system suddenly recognizes other chronic infection
- Good: HAART is the only cure for cryptosporidiosis, CMV retinitis, cryptococcal meningitis, *Mycobacterium avium-intracellulare* complex (MAI), PML (JC virus); improves prognosis in lymphoma or Kaposi's sarcoma
- Bad: Too much inflammation in the wrong place- TB, MAI, cryptococcal meningitis, CMV retinitis

Immune reconstitution in TB

- Usually in first few weeks of HAART
- Sometimes occurs with TB therapy alone
- Fever, worsening pulmonary symptoms, compression of airways with nodes, pleural effusion, worsening CXR
- Prevention: Start TB therapy first
- Treatment: Prednisone 1-2 mg/kg/d X 1-2 weeks if severe

WHO recommendations for treatment of HIV/TB co-infection in adults- 2003

- CD4 < 200 or extrapulmonary TB: Start TB treatment. Add HAART as soon as TB treatment well tolerated (in 2 weeks-2 months)
- CD4 200-350: Start TB treatment. Start HAART after initiation phase (if otherwise not urgently needed)
- CD4 >350: Start TB treatment. May defer HAART if no stage IV symptoms.
- No CD4 available: Start TB treatment, consider HAART if other HIV symptoms, or on completion of TB therapy

Antiretrovirals and TB drugs

- Rifampin induces metabolism (reduces drug exposure to % indicated)
 - ZDV (47%): ? Increase dosage 50+%
 - ABC: ? (No data but moderate effect expected)
 - NVP (65%): Use EFV (or increase dosage?)
 - EFV (78%): May increase dosage by 20-25%
 - NFV (17%): Do not use
 - LPV/r (25%): Do not use or add extra RTV (LPV 400/RTV 400 in adults is good) or increase dosage
 - IDV (8%) or IDV/r (15%): Do not use
- SQV/r gives good levels with rifampin BUT increases hepatic toxicity in adults

What is the most common complication of HAART?

Resistance