

Pharmacokinetics Disease; Managing adverse effects & drug drug interactions

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Introduction

- Almost twenty years into the global HIV pandemic, a cure still remains elusive
- HAART regimens have brought hope, but adverse effects remain to be a major obstacle
- The increasing number of ARV drugs comes with new adverse effects
- Suppression of HIV within 6-12 months:
 - 70-90% in clinical trials
 - 50% in clinical practice

Currently available options for HAART regimens

- NRTIs (Zidovudine, stavudine, lamivudine, zalcitabine, didanosine, abacavir)
- NNRTIs (niverapine, delavirdine, efavirenz)
- PIs (ritonavir, indinavir, nelfinavir, lopinavir, amprenavir)
- Drugs for opportunistic infections & co morbid disorders



Need for effective strategies

- To manage adverse drug reactions
 - eg. Is there need to stagger some of the drugs?
 - Will reduction of dose help?
- This will encourage patients' ultimate adherence to a given HAART regimen

What is the scope of the Problem?

- Drug-specific AEs
 - NRTIs
 - NNRTIs
 - PIs
- Broad treatment-related AEs
 - Lipodystrophy
 - Metabolic abnormalities
 - Bone disease

Importance of Adequate knowledge on HAART & AEs

- Increasing complexity of HAART
 - Increasing number of agents
 - Drug-drug interactions
- Being able to identify AEs and suggesting what to do will help patients understand and tolerate difficult effects of certain agents
 - *eg.* ABC, NVP, EFV
- Helping patients to tolerate the maximum number of agents preserves options for the future for that particular patient

General Considerations

- Need to help patients maintain good health to:
 - prevent specific nutritional disorders
 - help tolerate medication side effects
 - improve immune status and well being
 - cut down the number and cost of medications

What should we do regarding AEs?

- Important to discuss potential adverse effects with patients
- Important to support patients using HAART for the first time. Indicate need to discuss emerging AEs with a pharmacist/doctor and not making own decision to stop medication
- Indicate need for frequent laboratory tests to monitor Changes in blood (CBC, blood chemistry), Liver function (AST, ALAT)
- This initial interaction will have a lot of influence on compliance to HAART regimens

Nucleoside Analogs (NRTIs)

■ Class adverse rxns

- GI disturbances: Nausea, vomiting (Food reduces GI disturbances)

**Food has no effect on bioavailability (All can be taken with or without food)

- Malaise (asthenia)
- Nucleosides that have abbreviations beginning with “d” (dideoxynucleosides) eg ddI, ddC and d4T are all associated with pancreatitis and peripheral neuropathy
- lactic acidosis (thought to be due to drug-induced mitochondrial toxicity)

Zidovudine (Retrovir, AZT)

Primary side effects: short term

- Initial nausea, headache, rash
- Ongoing nausea
- Ongoing “dysphoria”

Primary side effects: long term

- Bone marrow suppression (Anemia, neutropenia, granulocytopenia)
- usually noticed by 6 weeks
- blue-gray nail discoloration (melanonychia)

D-Drugs

- d4T (Zerit[®], stavudine)
 - Peripheral neuropathy
 - Hepatitis
 - Pancreatitis
 - Lactic acidosis
 - GI disturbance (nausea, vomiting)
 - Lipodystrophy
 - rash

D-Drugs

- Didanosine (ddl; Videx) (Videx EC)
 - Peripheral neuropathy
 - Pancreatitis
 - Lactic acidosis
 - Hepatitis
 - Lipodystrophy
 - GI disturbances

D-Drugs

- Zalcitabine (ddC; Hivid)
 - peripheral neuropathy
 - Hepatotoxicity
 - Lactic acidosis
 - Lipodystrophy
 - Mouth ulcers (stomatitis)
 - GI disturbances

D-Drugs

- Lamivudine (3TC; Epivir)
 - peripheral neuropathy
 - Lactic acidosis
 - GI disturbances
 - Fatigue, headache, insomnia, fever

Abacavir

- Hypersensitivity Rxn
 - warn but do not scare the patient; Describe the syndrome (indicate need to seek advice before stopping medication)
 - re: reintroduction (strictly not allowed)
- Rare cases of Stevens-Johnson syndrome
- Peripheral neuropathy
- Lactic acidosis
- GI upsets

Non-Nucleoside RTIs (NNRTIs)

■ Nevirapine

□ Rash

- Management takes frequent monitoring to assess whether patient may continue or must stop, rash in up to 1/3 of patients
- Keep in mind concern of “Stevens-Johnson” with desquamation of cutaneous and mucus membranes (<1%)

□ Hepatitis

- May develop relatively quickly after start
- Pay particular attention to co-infected patients with Hepatitis C in women

NNRTIs

■ Efavirenz

□ CNS Side Effects

- Dizziness, insomnia
- Vivid dreams (hallucinations)
- Depression
 - Think twice in patients with co morbid serious mental illness

□ hepatotoxicity

□ Rash

- Generally mild and self-limiting

■ Delavirdine

□ Rash similar to NVP

Protease Inhibitors (PIs)

- General: GI side effects
 - Size and number of pills
- But never forget: they first revolutionized HAART and currently clearly change progression rates to AIDS and death in the sickest patients, *ie*, CD4 <100
- Best absorbed when taken with food (except amprenavir - wth/wthought)
- All are highly protein bound (90-98%)

Indinavir

Nephrolithiasis (hydration needed) & Other renal issues

- “Retinoid Syndrome”
- Hyperlipidemia (particularly with RTV)
- elevated triglycerides, hyperglycaemia
- lipodystrophy
- Hyperbilirubinemia
- GI upsets & metallic taste

Nelfinavir

■ Diarrhea!

- Usual course: after initial dosing, presents in intermittent pattern
- Best advice is to take after a substantial meal
- Usually not accompanied with any other complaint
- Responds to loperamide well, some use calcium carbonate
- Lipodystrophy
- hyperglycaemia

Saquinavir

- GI complaints: nausea, gas, bloating, cramps, and diarrhea
 - Symptomatic treatment
 - If occurs, becomes more tolerable over time
 - Amount of food prior to Rx
 - Lipodystrophy (elevated TGs, Hyperglycaemia)

Amprenavir

- Complaints

 - nausea, cramps, bloating, gas, and diarrhea

- Rash (small but important)

- Lipodystrophy

- Elevated TGs, hyperglycaemia

Ritonavir

- Intolerable taste & GI disturbances
- Combination with IDV, SQV, and LPV
 - allows for BID dosing (take with food)
- Hyperlipidemia & hyperglycaemia
- Hepatitis, lipodystrophy, asthenia
- Drug-drug interactions—many!

Kaletra®

- First “fixed-dose” PI containing RTV/ LPV; gets boosted to very high blood levels
- GI side effects relatively mild, mostly “bloating and gas”
- Taken with food

Drug interactions

- Pharmacokinetic
 - Pharmacodynamic
 - Enhancement of toxicity

- Influenced by: nutritional status, Age of the patient, Gender
 - Genetic predisposition (rate of drug metabolism)
 - Hepatic, renal or cardiac impairment
 - Smoking; “recreational drugs” or alcohol

NRTIs & NtRIs

ZDV combined with:

- Probenecid:-Inhibit glucuronidation and renal excretion of ZDV
- Atovaquone: Inhibit glucuronidation
- Anti-TBs (Rifamycins): Increase metabolism
- Ganciclovir & flucytosine: Profound bone-marrow suppression
- ddl, ddC, 3TC: Synergistic (useful for HAART combinations (AZT can be substituted by d4T))

Protease inhibitors (PIs)

■ All PIs:

- all are substrates & inhibitors CYPs
- Ritonavir >indinavir = nelfinavir > saquinavir
- Those on the left increase B. levels of those on the right
- Increase blood levels of other drugs eg. amphetamine (fatal overdose)

Saquinavir (SQV) with

- Ritonavir, ketoconazole, ranitidine:
-less saquinavir needed
- Rifamycins (rifampicin, rifabutin)
- Anticonvulsants (phenobarbitone, Phenytoin, carbamazepine), dexamethasone
- Midazolam & triazolam
-reduce levels of SQV; require dose increase
- Astemizole, cisapride, terfenadine
-arrhythmias & prolonged sedation (fatal)

Ritonavir (RTV) with

- Inhibit metabolism of drugs by CYP 3A4 & 2D6
- Increase metabolism by glucuronyl transferase (reduce R. bioavailability)
- Inhibit metabolism of:
 - clarithromycin, despiramine, ethinyl estradiol, rifamycins, sulphamethoxazole, trimethoprim
- INV, SQV, LPV/APV
 - elevate plasma levels; possibility of dose reduction

Indinavir & nelfinavir

- **Plasma levels increased by:**
 - cimetidine, quinidine, Fluconazole, ketoconazole, trimethoprim/sulphamethoxazole
- **Increase plasma levels of**
 - saquinavir
 - terfenadine, astemizole, cisapride, midazolam, triazolam (cardiac arrhythmias & prolonged sedation)

NNRTIs

Nevirapine:

- Induces CYP 3A4; increase clearance of other drugs
- Increase clearance of AZT by glucuronyl transferase
- Not given with metformin (lactic acidosis)

Efavirenz:

- Increase metabolism of LPV/RTV (need to increase dose)

Conclusion

- Knowledge and “wisdom” play a large role in helping patients reach their goals as to managing AEs
- You can not give the much needed support without adequate knowledge
- Side effect management is the key element for maintaining high rate of adherence, thus frequent monitoring, including laboratory, is necessary
- By maximizing support for patient to tolerate each potentially troublesome agent, you maximize the patient’s long-term options