Managing ARV regimen failure in the HIV infected child

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Case study:

- Thabo is a twelve year old boy. He has been on ARV's (3TC, stavudine and efavirenz) for 3 years. He is growing well and on clinical examination he has no abnormalities
- BUT
- His viral load is 5300
- Is he failing his ARV regimen; do we need to change his treatment?

Definition of a failing regimen:

- *Older definitions:*
- 1)Clinical-*Tuberculosis (new opportunistic infections or disease progression)*
- 2)Immunological-*immunological non-responders (Cd4 should ↑by5% or 50 after one year)*
- *Both clinical and immunological failure develops slowly and after having virological failure for many years=only used where viral load monitoring not done*
- 3)Virological failure

Virological failure:

- 2 definitions:
- Non-responder: VL > 400 after 6 months and higher than 0 after 12 months on treatment
- Viral rebound: a viral load of > 1000 copies/ml on 2 separate occasions 3 months apart after previously having had undetectable viral loads

Causes of virological failure

- Blips : intercurrent infection , immunisation
- Non-adherence
- Viral resistance
- Inferior Arv regimens
- Wrong dosage
- Concurrent infections-TB
- Medication interaction-rifampicin, herbal medication
- Malabsorption
- Transmitted resistance

3 MOST COMMON REASONS:

- Non-adherence
- TB
- Resistance to ARV's

Certain Arv's more problematic with regards to resistance mutations

- 3TC /FTC- one mutation
- Efavirenz, nevirapine-one mutation and you lose both=whole NNRTI class
- Protease inhibitors seldom have resistance mutations against them

Resistance Consequences of Initial Regimen Failure: ACTG 5142

- Genotypic resistance data (180/227 patients with virologic failure)
  - Incidence of any drug resistance mutation or 2-class resistance higher in patients with virologic failure on EFV-containing regimens

Characteristic	EFV + NRTIs (n = 250)	LPV/RTV + NRTIs (n = 253)	EFV + LPV/RTV (n = 250)
Virologic failures, n	60	94	73
Genotypic assays, n	46	78	56
Any mutation (except minor protease mutations), %*	48	21	70
NRTI mutations, %	30	19	11
NNRTI mutations, %†	43	3	66
Mutations in 2 drug classes, %‡	26	1	7

*EFV + LPV/RTV vs LPV/RTV + NRTIs, $P < .001$; EFV + NRTIs vs LPV/RTV + NRTIs, $P = .002$
†LPV/RTV + NRTIs vs EFV + NRTIs or EFV + LPV/RTV, $P < .001$
‡LPV/RTV + NRTIs vs EFV + NRTIs, $P < .001$; EFV + NRTIs vs EFV + LPV/RTV, $P = .01$

Riddler SA, et al. N Engl J Med. 2008;358:2095-2106.

Practical implication:

- Child older than 3 years : on 3TC ,abacavir or stavudine and efavirenz =2 medications in his regimen are VERY susceptible to resistance
- Child younger than 3: on 3TC, abacavir or stavudine and Kaletra (protease inhibitor)= only one medication susceptible to resistance, protease inhibitor very effective

Distinguishing between non-adherence and resistance

	Thabo-12 years old-on 3TC,ABC,EFV for 3 years	Kagisho-5 years old-on 3TC, ABC, EFV for 2 years	Lerato-18 months old-on 3TC,ABC,Kaletra for one year
Viral load 12 months ago	1000	undetectable	Baseline > 10 million
Viral load 6 months ago	3200	1500	1500
Viral load last month	5000	25 000	25 000

Causes and management of non-adherence

- Fear and ignorance
- Practicalities
- Denial
- Caregiver sick or dies
- Health system failure
- Teenagers
- Intolerable side-effects
- Therapeutic drug monitoring
- DOTS

Mutated HIV versus wild-type C HIV

- Mutated HIV is MUCH weaker than wild type virus
- Less likely to develop opportunistic infections or disease progression
- Not as easily transmitted
- Can live well for MANY years with mutated HIV

Managing HIV with resistance mutations:

- Very complex
- Making the wrong choice for the second regimen may cause a patient to loose all future hope of a regimen that suppresses replication
- Should only be treated by a doctor with expertise ???

HIV RESISTANCE GENOTYPING

- Viral load must be above 1000 copies/ml
- Not routinely available-R4500
- Takes months to get the result-? Clinical use
- Can only detect the mutations aimed at the Arv's the patient has been taking during the previous month
- Can also only detect the mutation if present in more than 20% of the viruses
- WILL not show previously acquired mutations (e.g. against PMTCT nevirapine)
- Most useful for excluding drugs, wont necessarily indicate which will work

The child who fails a protease inhibitor regimen MUST have genotyping done and should only be managed by a HIV specialist

- Was most likely exposed to ritonavir as only protease inhibitor in an older regimen

The child who fails the standard SA first regimen on Efavirenz

- If the child is not switched early, he is at risk of acquiring TAM's (thymidine analogue mutations=AZT/D4T/DDI/tenofovir/abacavir)
- BUT if the resistance is detected early the child will most likely have 2 clinically significant mutations
- K103N=confers resistance to efavirenz and nevirapine
- M184V=confers resistance to 3TC/FTC

M184V MUTATION=THE SILVER LINING

- Develops if there is resistance to 3TC (first mutation)
- Virus with this mutation has reduced fitness
- M184V mutation may reverse resistance to AZT,d4T and tenofovir
- Can add 3TC to a regimen-even though there is documented resistance- to maintain this weaker virus
- Abacavir can also maintain this mutation

Switching regimens:

- 2nd line regimens are more difficult to take
- This patient has already failed on a simple first line regimen
- MUST address adherence issues BEFORE any changes are made
- If a child fails his second regimen he is in deep trouble!!

When switching regimens:

- Never switch or add only one medication in a failing regimen
- When interpreting resistance report; remember that resistance to previously taken Arv's will not show up
- Consider cross-resistance between Arv's-AZT/D4T; NVP/EFV; amongst protease inhibitors
- Certain ARV's should not be used together: tenofovir and abacavir/ddI ; AZT and D4T; D4T and ddI
- Previous exposure to only ritonavir= will not show up on genotyping BUT will have lost all protease inhibitors
- At least 2, preferable 3 new active drugs
- Chance of success improve if a new drug class is used

Resistance associated RT Mutations: M184V*, G190E

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
abacavir (ABC)	No Evidence of Resistance
didanosine (ddI)	No Evidence of Resistance
lamivudine (3TC)/emtricitabine (FTC)	Resistance
stavudine (d4T)	No Evidence of Resistance
tenofovir (TDF)	No Evidence of Resistance
zidovudine (AZT)	No Evidence of Resistance

NonNucleoside RT Inhibitors	Resistance Interpretation
efavirenz (EFV)	Resistance
nevirapine (NVP)	Resistance

Child failing 3TC and abacavir and efavirenz with only a M184V NRTI mutation:

- Since both maintain the M184V mutation you can use either lamivudine or abacavir in your second regimen; combined with a different active drug
- Good choices: AZT and abacavir
- Tenofovir and lamivudine
- lamivudine and AZT
- Third drug will then be a protease inhibitor: kaletra (ritonavir boosted lopinavir)

Resistance associated RT Mutations: D67N, K70R, K103N, V106M, M184V*, K219Q, F227L

Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
abacavir (ABC)	No Evidence of Resistance
didanosine (ddI)	No Evidence of Resistance
lamivudine (3TC)/emtricitabine (FTC)	Resistance
stavudine (d4T)	*Possible Resistance*
tenofovir (TDF)	No Evidence of Resistance
zidovudine (AZT)	*Possible Resistance*

NonNucleoside RT Inhibitors	Resistance Interpretation
efavirenz (EFV)	Resistance
nevirapine (NVP)	Resistance

Resistance associated PR Mutations: K20R*, M36I*, H69K, L89M, I93L*

Protease Inhibitors	Resistance Interpretation
amprenavir (APV)/fosamprenavir (FPV)	No Evidence of Resistance
APVr or FPVr **	No Evidence of Resistance
atazanavir (ATV)	No Evidence of Resistance
ATVr **	No Evidence of Resistance
darunavir + ritonavir (DRVr)	No Evidence of Resistance
indinavir (IDV)	No Evidence of Resistance
IDVr **	No Evidence of Resistance
lopinavir + ritonavir (LPVr)	No Evidence of Resistance
nelfinavir (NFV)	No Evidence of Resistance
saquinavir + ritonavir (SQVr)	No Evidence of Resistance
tipranavir + ritonavir (TPVr)	No Evidence of Resistance

** Protease inhibitors administered with low-dose ritonavir for pharmacological boosting.

CASE STUDY

- 6 years old
- Started on AZT/ddI/NVP Jan 2005
- Changed to d4T/3TC/EFV August 2007 because of poor response

Date	May 07	August 07	Oct 07	Feb 08	May08	June 08	Aug 08
Age	4			5			
CD4	632			356	505		398
Cd4 %	21.5		20	13.2	15.3		18.2
Viral load	2.4 million	510 000	77000	150 000	85000	58 000	39000
ART	ddI,AZT,NVP	3TC,d4T,EFV					

GENOTYPING:

- NRTI resistance mutations:M41L,E44D,T69D,V118I,M184V,L210W,T215Y,K219R
- NNRTI Resistance Mutations:V106L, Y188L
- PI Resistance Mutations:T12S,I15V,L19I,L63P,H69K,K70Q,V77I,L89M,I93L
- Susceptible: All PI's
- Low level-resistance: Etravirine
- Intermediate resistance: tenofovir
- High level resistance: 3TC,Abacavir,ddI,d4T,AZT,FTC,NVP,EFV

Holding regimens

- 3TC monotherapy to maintain the mutated virus
- Goal is not to suppress viral replication but to win time until issues are resolved
- Non-adherence unable to resolve
- Only if CD4 is reasonable and not if nadir Cd4 is low

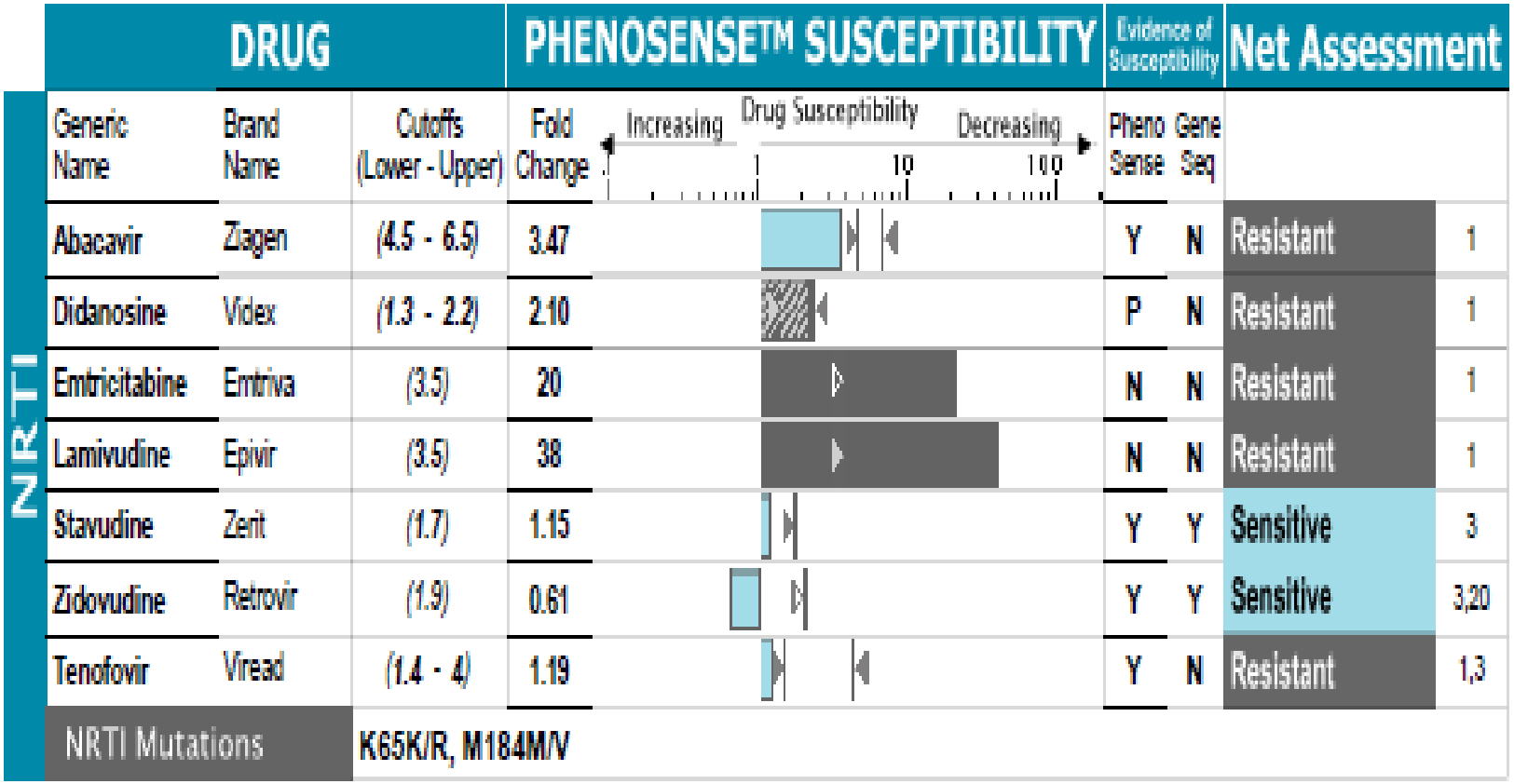
Bridging regimens:

- If CD4 is too low for monotherapy
- Patient has resistance to all NRTI's
- Await availability of new drugs
- E.g. AZT/3TC/ABC/TDF
- Once Cd4 drops to below 200-350 or child develops symptoms=need a definitive regimen

New ARV's

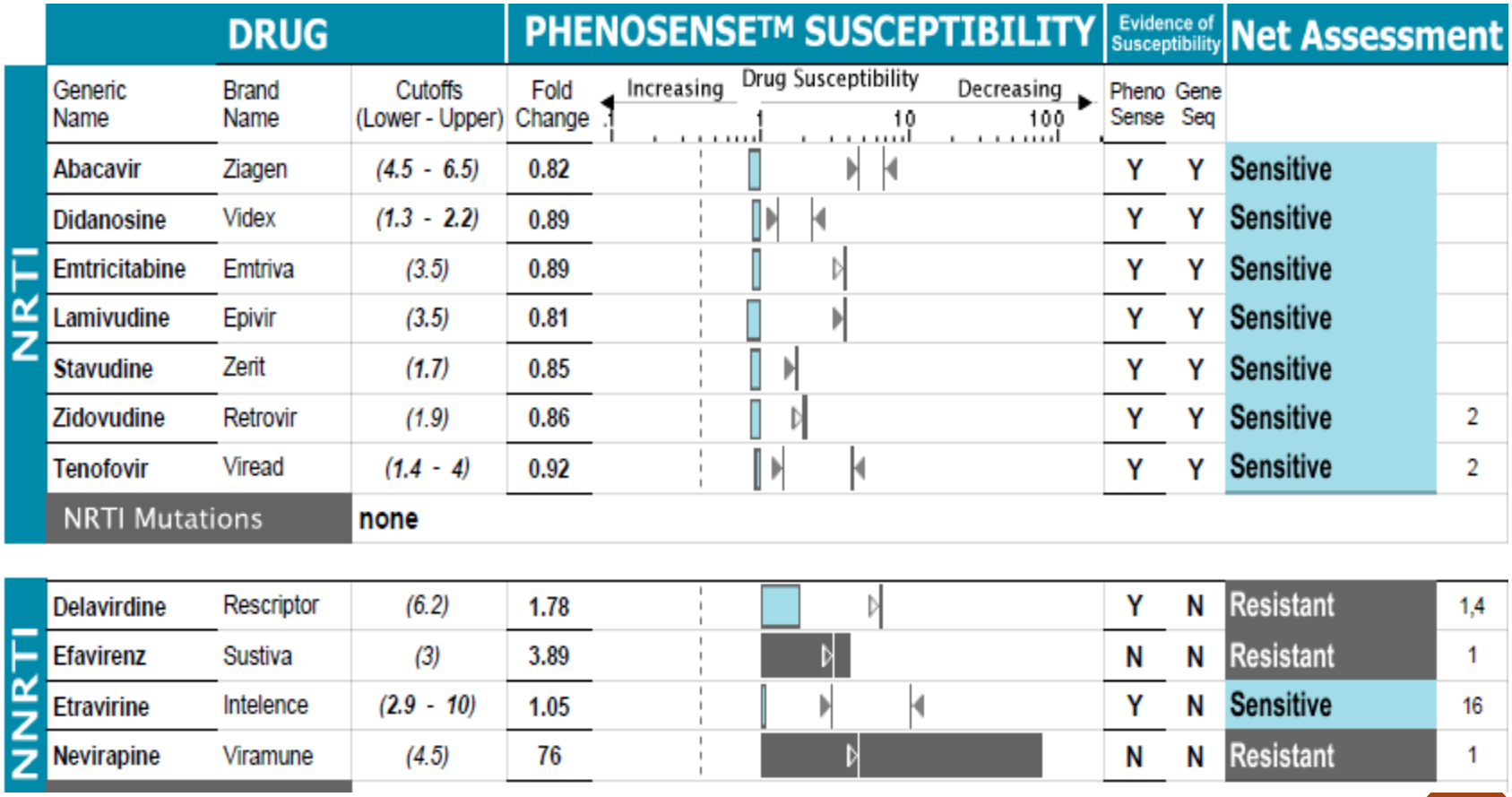
- *Nucleotide* reverse transcriptase inhibitors: tenofovir
- New protease inhibitors- tipranavir, darunavir (might work if many PI mutations), atazanavir
- New NNRTI- etravirine (not always resistant if previously on EFV/NVP)
- *New classes-* Raltegravir (integrase inhibitor) BUT also easily develops mutations
- Enfuvirtide (HIV entry inhibitor)
- Maraviroc (CCR5 inhibitor) only works for certain strains of HIV

TRANSMITTED RESISTANCE



	DRUG			PHENOSENSE™ SUSCEPTIBILITY	Evidence of Susceptibility		Net Assessment	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Pheno Sense	Gene Seq		
NRTI	Abacavir	Ziagen	(4.5 - 6.5)	3.47	Y	N	Resistant	1
	Didanosine	Videx	(1.3 - 2.2)	2.10	P	N	Resistant	1
	Emtricitabine	Emtriva	(3.5)	20	N	N	Resistant	1
	Lamivudine	Epivir	(3.5)	38	N	N	Resistant	1
	Stavudine	Zerit	(1.7)	1.15	Y	Y	Sensitive	3
	Zidovudine	Retrovir	(1.9)	0.61	Y	Y	Sensitive	3,20
	Tenofovir	Viread	(1.4 - 4)	1.19	Y	N	Resistant	1,3
	NRTI Mutations		K65K/R, M184M/V					

Consequences of nevirapine PMTCT



	DRUG			PHENOSENSE™ SUSCEPTIBILITY		Evidence of Susceptibility		Net Assessment	
	Generic Name	Brand Name	Cutoffs (Lower - Upper)	Fold Change	Increasing Drug Susceptibility Decreasing (.1 / 1 / 10 / 100)	Pheno Sense	Gene Seq		
NRTI	Abacavir	Ziagen	(4.5 - 6.5)	0.82		Y	Y	Sensitive	
NRTI	Didanosine	Videx	(1.3 - 2.2)	0.89		Y	Y	Sensitive	
NRTI	Emtricitabine	Emtriva	(3.5)	0.89		Y	Y	Sensitive	
NRTI	Lamivudine	Epivir	(3.5)	0.81		Y	Y	Sensitive	
NRTI	Stavudine	Zerit	(1.7)	0.85		Y	Y	Sensitive	
NRTI	Zidovudine	Retrovir	(1.9)	0.86		Y	Y	Sensitive	2
NRTI	Tenofovir	Viread	(1.4 - 4)	0.92		Y	Y	Sensitive	2
NRTI	NRTI Mutations		none						
NNRTI	Delavirdine	Rescriptor	(6.2)	1.78		Y	N	Resistant	1,4
NNRTI	Efavirenz	Sustiva	(3)	3.89		N	N	Resistant	1
NNRTI	Etravirine	Intelence	(2.9 - 10)	1.05		Y	N	Sensitive	16
NNRTI	Nevirapine	Viramune	(4.5)	76		N	N	Resistant	1

HIV DISEASE IN THE FUTURE

- I think HIV will change from a disease where we have masses of sick hospitalised patients
- To masses of patients treated at outpatient departments
- Many with complex resistance
- All health workers will have to have some knowledge on managing ARV treatment failure