New Drugs & Their Role in Pediatric HIV

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Disclosure of Financial Relationships

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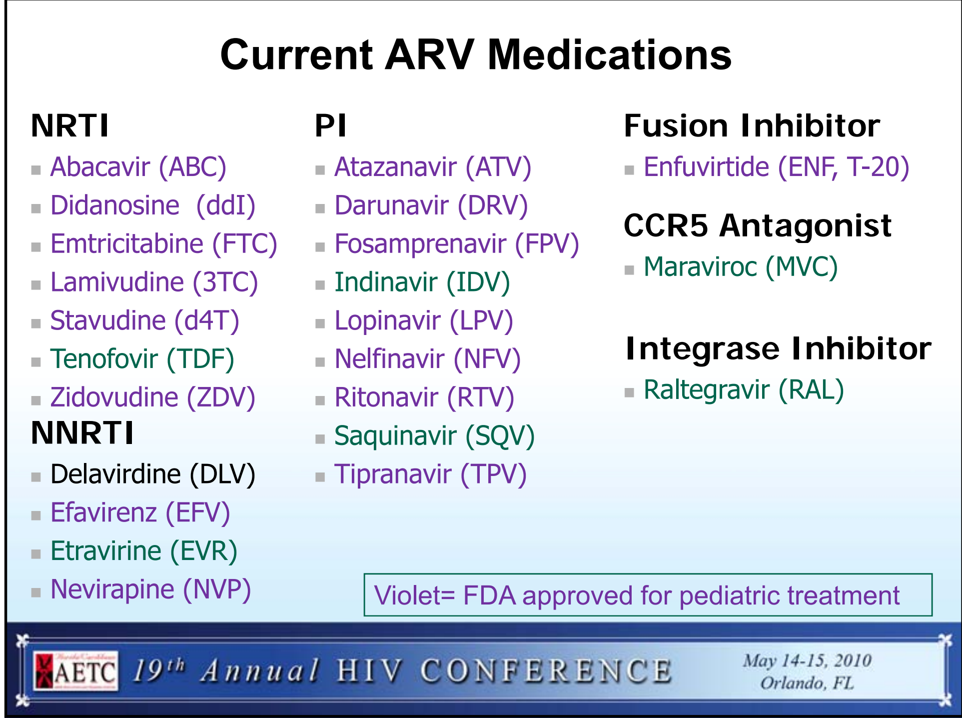
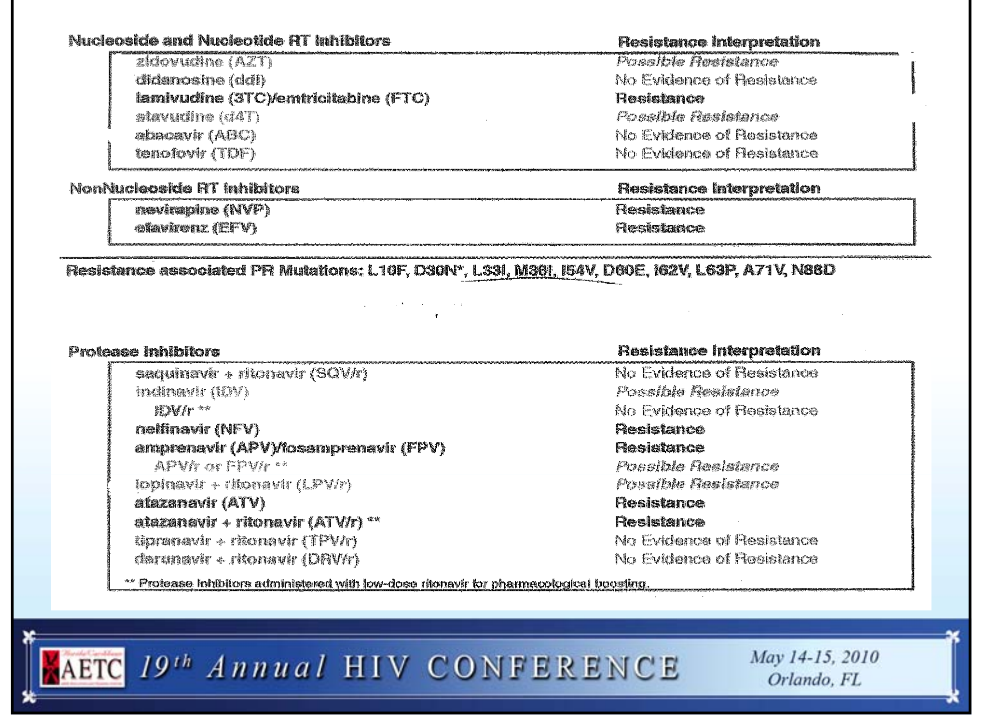
Objectives

- Briefly describe the new drugs that have become available over the last 5 years with particular application to pediatrics
- Discuss the issues unique to children and adolescents when recommending and treating with HAART
- Discuss a few challenging cases

New Drugs

- Fusion/Entry Inhibitor- Maraviroc (Selzentry™)
- Non Nucleoside Reverse Transcriptase Inhibitor-Etravirine (Intelence™)
- Integrase Inhibitor- Raltegravir (Isentress™)
- Protease Inhibitor- Darunavir (Prezista™)





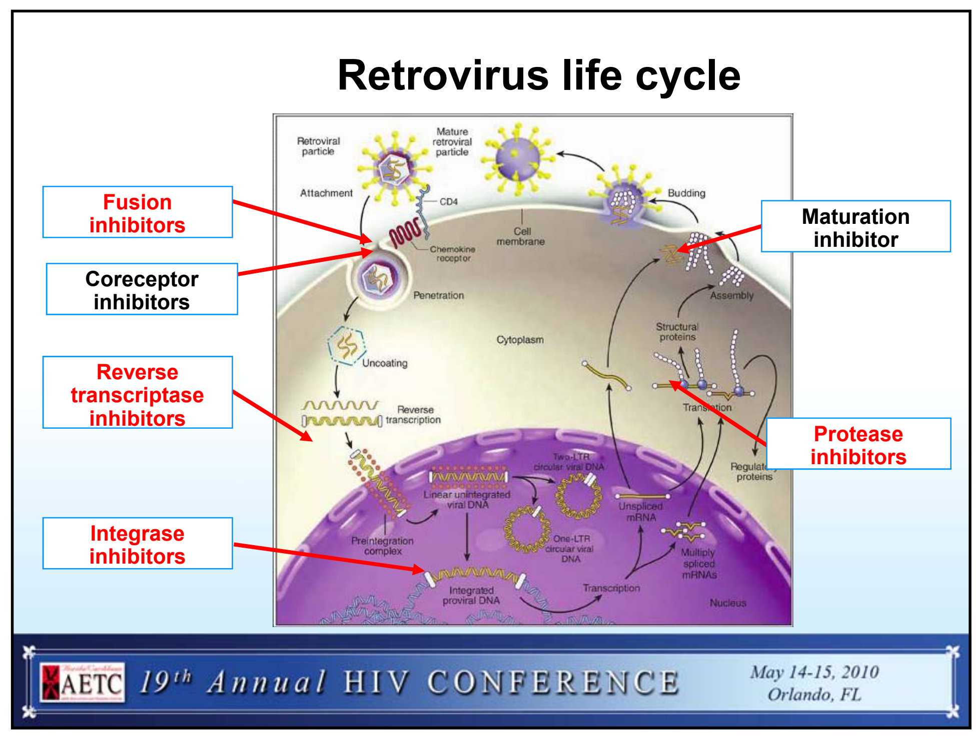
Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
zidovudine (AZT)	*Possible Resistance*
didanosine (ddI)	No Evidence of Resistance
lamivudine (3TC)/emtricitabine (FTC)	**Resistance**
stavudine (d4T)	*Possible Resistance*
abacavir (ABC)	No Evidence of Resistance
tenofovir (TDF)	No Evidence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

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

Resistance associated PR Mutations: L10F, D30N*, L33I, M36I, I54V, D60E, I62V, L63P, A71V, N88D

Protease Inhibitors	Resistance Interpretation
saquinavir + ritonavir (SQV/r)	No Evidence of Resistance
indinavir (IDV)	*Possible Resistance*
IDV/r **	No Evidence of Resistance
nelfinavir (NFV)	**Resistance**
amprenavir (APV)/fosamprenavir (FPV)	**Resistance**
APV/r or FPV/r **	*Possible Resistance*
lopinavir + ritonavir (LPV/r)	*Possible Resistance*
atazanavir (ATV)	**Resistance**
atazanavir + ritonavir (ATV/r) **	**Resistance**
tipranavir + ritonavir (TPV/r)	No Evidence of Resistance
darunavir + ritonavir (DRV/r)	No Evidence of Resistance

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



Retrovirus life cycle
Fusion inhibitors
Coreceptor inhibitors
Reverse transcriptase inhibitors
Integrase inhibitors
Maturation inhibitor
Protease inhibitors
Retroviral particle
Mature retroviral particle
Attachment
CD4
Budding
Chemokine receptor
Cell membrane
Penetration
Assembly
Cytoplasm
Structural proteins
Uncoating
Reverse transcription
Two-LTR circular viral DNA
Linear unintegrated viral DNA
Unspliced mRNA
Preintegration complex
One-LTR circular viral DNA
Multiply spliced mRNAs
Integrated proviral DNA
Transcription
Nucleus
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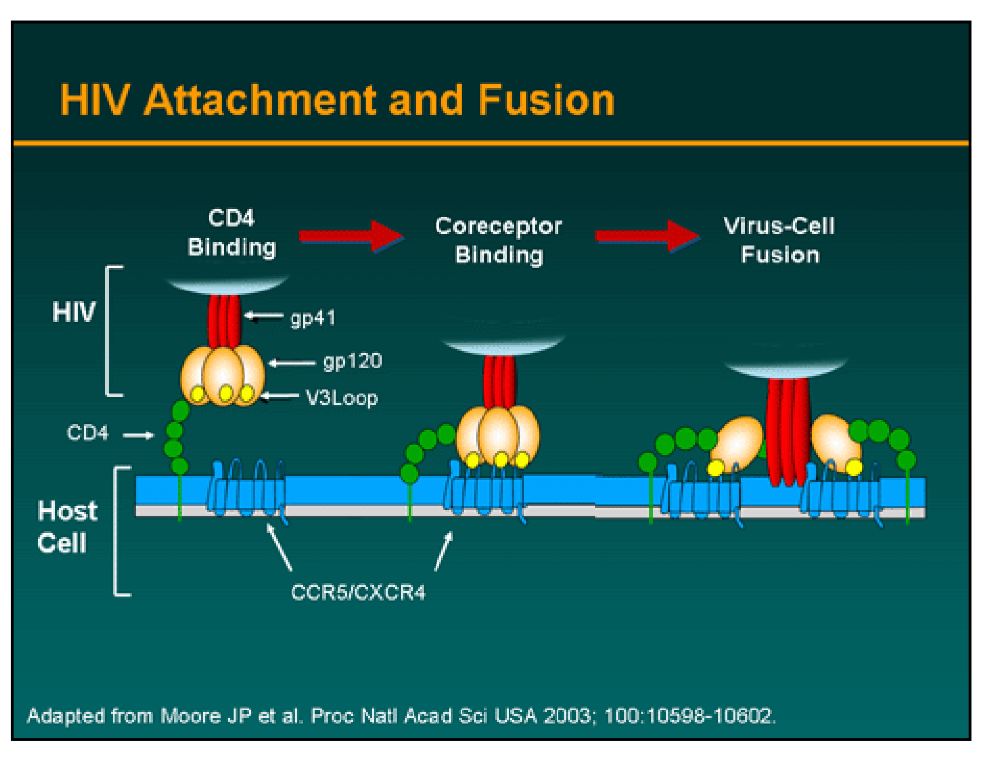


HIV Attachment and Fusion
CD4 Binding
Coreceptor Binding
Virus-Cell Fusion
HIV
gp41
gp120
V3Loop
CD4
Host Cell
CCR5/CXCR4
Adapted from Moore JP et al. Proc Natl Acad Sci USA 2003; 100:10598-10602.

Darunavir (Prezista™)

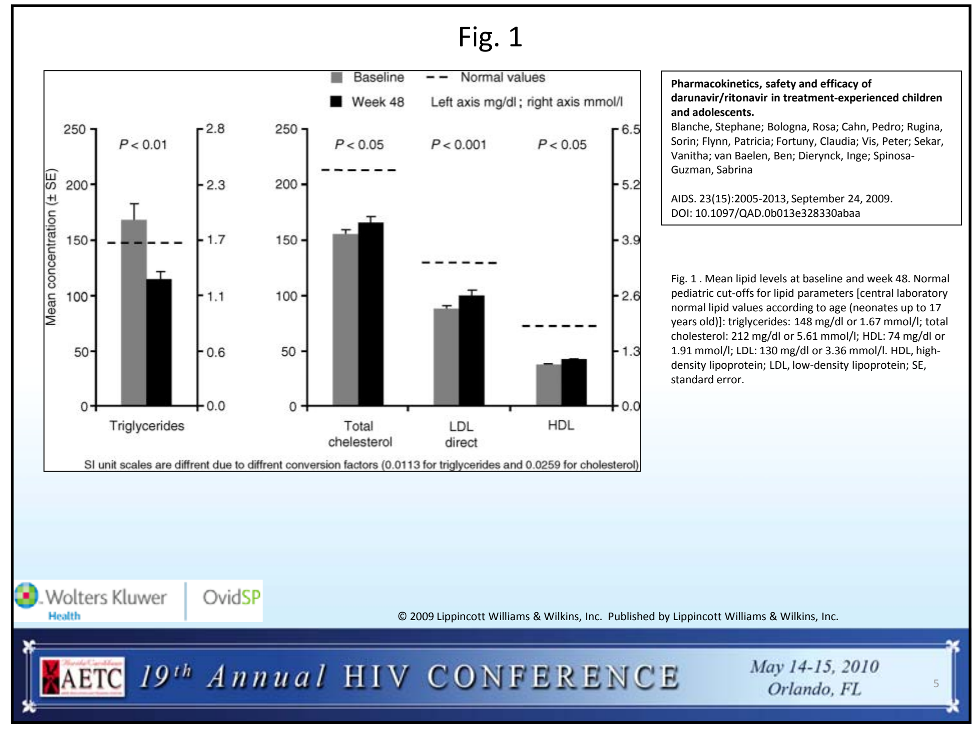
- Approved by FDA 6-23-2006
- Second generation PI
- Initially approved for use by treatment-experienced adolescent and adult patients ≥ 18 years
- Subsequently (12/08) approved for children ≥ age 6 –limiting factor high pill burden in children < 40 kg

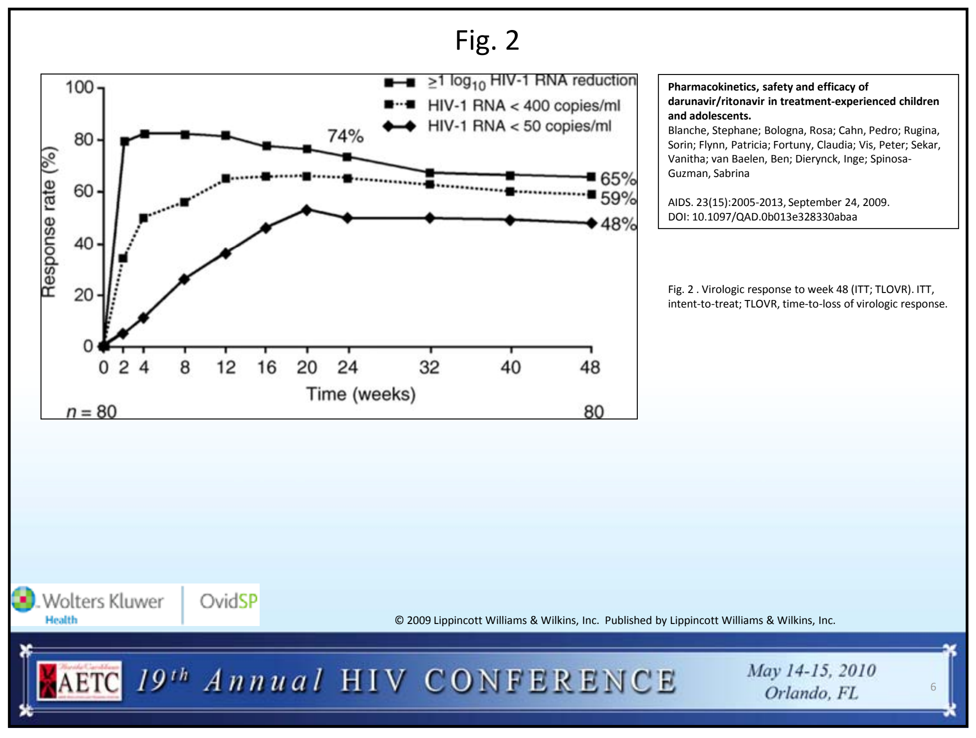
Darunavir - Pharmacokinetics

- Inhibits cleavage of HIV-encoded Gag-Pol polyproteins
- Cmax approximately 30% higher when taken after a meal compared to fasting
- 95% protein bound
- Metabolism: extensively by CYP enzymes, predominantly CYP3A
- Pregnancy Category: B

Darunavir

- Approval for pediatric patients based on 24 week data from TMC 114-C212 (DELPHI Trial)
- Phase 2 open label trial of HIV infected treatment experienced pediatric patients between 6-17 years of age and weighing at least 20 kg (44 lbs)





DELPHI Trial

- Conclusion of the 48 week f/u data : in treatment-experienced children and adolescents, DRV/r showed comparable results to adults with appropriate dose selection, favorable safety and tolerability, improved body weight and significant virologic response.
- DRV/r is a valuable therapeutic option for this population.

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Darunavir

- Not recommended for use in initial therapy, to be used with other effective antiretroviral agents
- Should not be used without ritonavir
- Darunavir may be given with atazanavir but not other protease inhibitors. Maraviroc must be decreased when given with darunavir.
- Multiple drug interactions: should not be used with carbamazepine, phenobarbital, phenytoin, St. John's wort, and rifampin

Darunavir - Adverse Drug Effects

- Most common ADEs: diarrhea, nausea, headache, nasopharyngitis
- Severe skin reactions, including erythema multiforme and Stevens-Johnson Syndrome, reported
- Also reported: high lipids, decreased WBCs, fever, elevated transaminases (25% incidence of grade 3 or 4 lab abnormalities)
- Not well studied in patients with chronic hepatitis

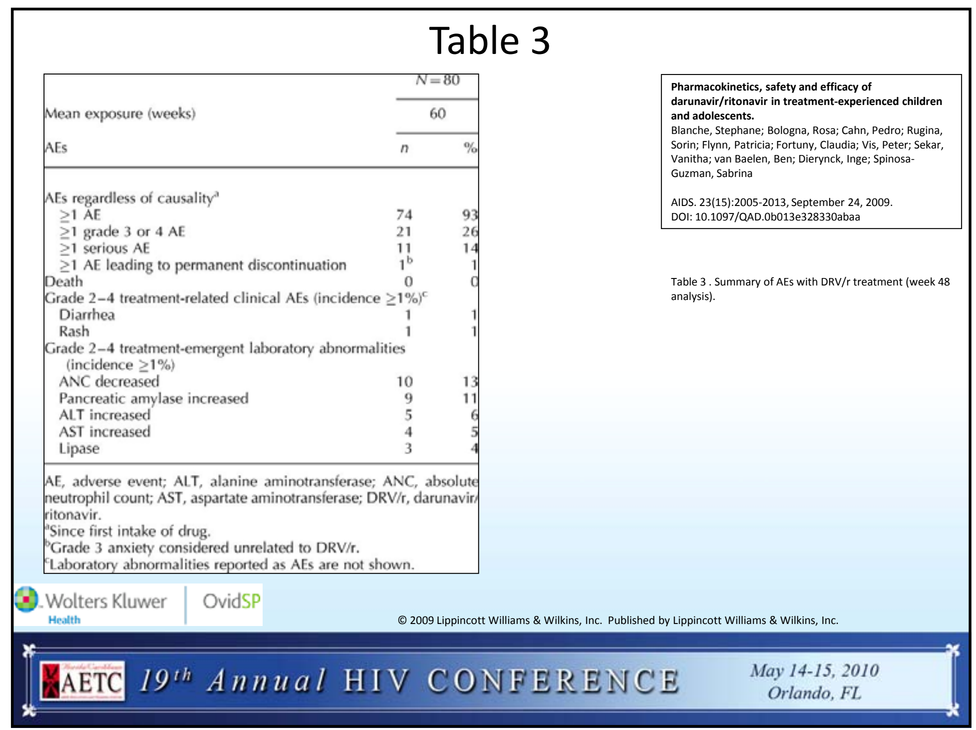

Table 3

	N = 80	
Mean exposure (weeks)	60	
AEs	n	%
AEs regardless of causality[a]		
≥1 AE	74	93
≥1 grade 3 or 4 AE	21	26
≥1 serious AE	11	14
≥1 AE leading to permanent discontinuation	1[b]	1
Death	0	0
Grade 2–4 treatment-related clinical AEs (incidence ≥1%)[c]		
Diarrhea	1	1
Rash	1	1
Grade 2–4 treatment-emergent laboratory abnormalities (incidence ≥1%)		
ANC decreased	10	13
Pancreatic amylase increased	9	11
ALT increased	5	6
AST increased	4	5
Lipase	3	4

AE, adverse event; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; DRV/r, darunavir/ritonavir.
[a]Since first intake of drug.
[b]Grade 3 anxiety considered unrelated to DRV/r.
[c]Laboratory abnormalities reported as AEs are not shown.

Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment-experienced children and adolescents.
Blanche, Stephane; Bologna, Rosa; Cahn, Pedro; Rugina, Sorin; Flynn, Patricia; Fortuny, Claudia; Vis, Peter; Sekar, Vanitha; van Baelen, Ben; Dierynck, Inge; Spinosa-Guzman, Sabrina

AIDS. 23(15):2005-2013, September 24, 2009.
DOI: 10.1097/QAD.0b013e328330abaa

Table 3 . Summary of AEs with DRV/r treatment (week 48 analysis).

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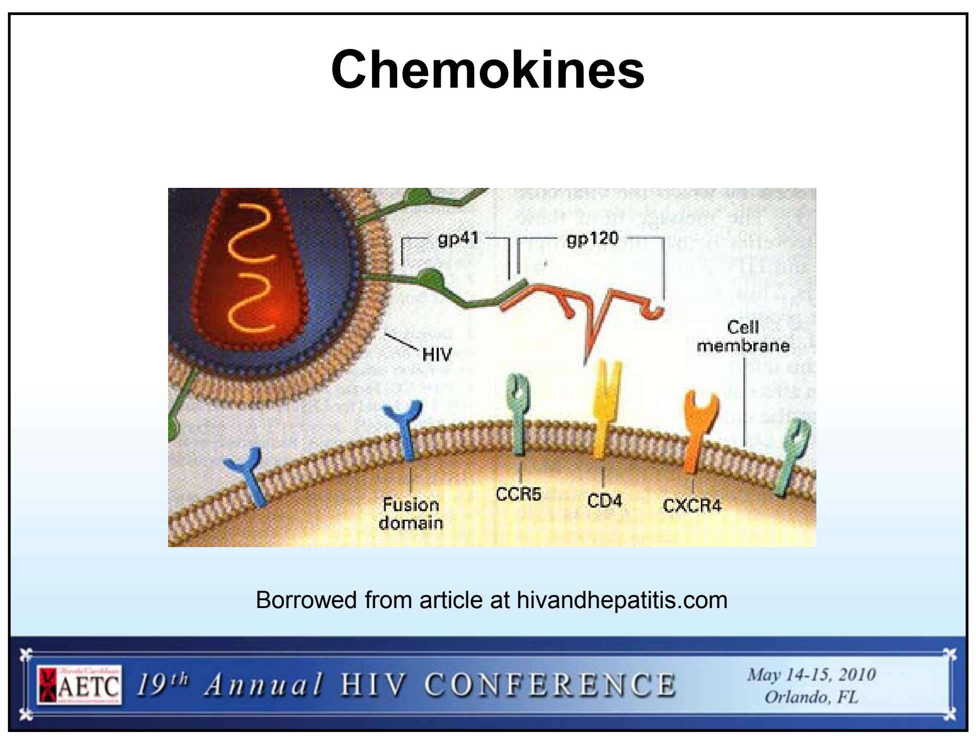
Darunavir - Resistance

- **Cross-resistance with other PIs seen**
  - DRV-resistant viruses not susceptible to AMP, ATV, IND, LPV, NLF, RTV, SQV
  - Limited cross-reactivity with tipranavir
- **Decreased response:**
  - 6-21 fold decrease if 3 of the following mutations present: S37N/D, R41E/S/T, K55Q, K70E, A71T, T74S, V77I, I85V

Fusion Inhibitor-Maraviroc

- FDA accelerated approval on August 6, 2007
- CCR5 co-receptor inhibitor
- Blocks cellular rather than viral function
- Approved in treatment experienced adolescents and adults ≥ 16 years with CCR5 tropic virus
- No efficacy with mixed or dual tropic virus

Chemokines



Borrowed from article at hivandhepatitis.com

Raltegravir (Isentress™)

- FDA approval on 10-12-2007
- First of the Integrase Inhibitors
- Approved for treatment-experienced adolescent and adult patients ≥ 16 years
- No significant drug-drug interaction with other ARVs
- Use with caution when administered with strong inducers of UGT, such as rifampin, which may lead to low levels

Etravirine (Intelence™)

- FDA approval on 1-18-2008
- First of the "Second Generation NNRTIs"
- Approved for treatment-experienced adult patients

Etravirine Resistance

- **Mutations:**
  - K103N – no effect
  - Worst responders had V179F*, Y181V*, Y106I, and V179O

* Also seen with EFV and NVP, always found together

Summary of New Drugs

- **Maraviroc:**
  - Must have CCR5-tropic virus on Trofile testing
- **Etravirine**
  - Still active with NNRTI-resistant strains with K103N
- **Raltegravir**
  - Minimal drug-drug interactions, active against resistant organisms
- **Darunavir ONLY ONE APPROVED FOR CHILDREN ≥ 6**
  - Good activity in deeply experienced patients; use cautiously in patients with chronic hepatitis.

ARV Initiation Considerations

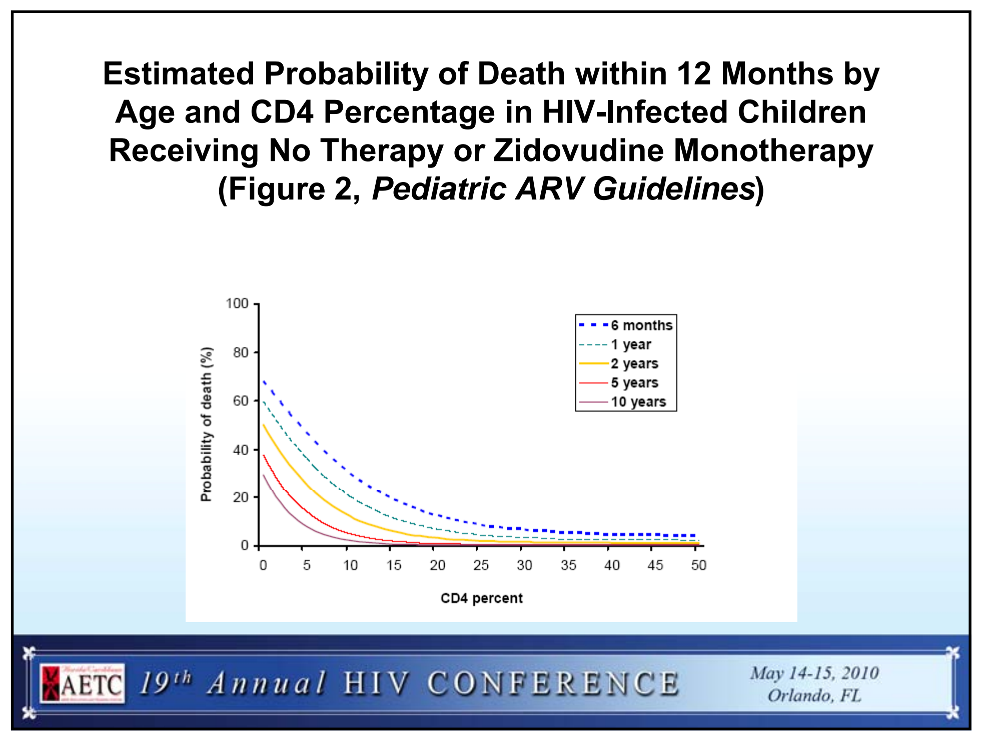
- **Disease severity and risk of progression, including:**
  - Presence or history of serious illness
  - CD4 count
  - HIV RNA level
- **Availability of appropriate and palatable drug formulations**
- **Complexity of regimen and potential adverse effects**
- **Effect of initial choice on later therapeutic options**

Unique Considerations for Infants, Children and Adolescents

- Age-specific differences in CD4 cell counts
- Changes in pharmacokinetic parameters with age (drug metabolism/clearance)
- Differences in clinical and virologic manifestations of perinatal infection
- Adherence to ART issues

Clinical Considerations

- HIV RNA and CD4 count or % are independently predictive of risk of disease progression
- Both help determine when to start and when to change ART
- CD4 count and % may be more useful than HIV RNA in evaluating risk in infants <12 months of age; in older children, both parameters are useful
- A 5-fold (.7 $\log_{10}$) change in HIV RNA copies/mL in infants or 3-fold (.5 $\log_{10}$) change in children aged ≥2 years is biologically and clinically significant



Indications for Initiation of ART in Children <12 Months of Age

Criteria	Recommendation
Regardless of clinical symptoms, immune status, or viral load	*Treat*

Indications for Initiation of ART in Children 1 to <5 Years of Age

Criteria	Recommendation
AIDS or significant HIV-related symptoms	***Treat***
CD4 <25%, regardless of symptoms or HIV RNA	***Treat***
Asymptomatic or mild symptoms *and* CD4 ≥25% *and* HIV RNA ≥100,000 copies/mL	***Consider***
Asymptomatic or mild symptoms *and* CD4 ≥25% *and* HIV RNA <100,000 copies/mL	***Defer***

Indications for Initiation of ART in Children ≥5 Years of Age

Criteria	Recommendation
AIDS or significant HIV-related symptoms	***Treat***
CD4 <350 cells/μL, regardless of symptoms or HIV RNA	***Treat***
Asymptomatic or mild symptoms *and* CD4 ≥350 cells/μL *and* HIV RNA ≥100,000 copies/mL	***Consider***
Asymptomatic or mild symptoms *and* CD4 ≥350 cells/μL *and* HIV RNA <100,000 copies/mL	***Defer***

Initial Treatment: NNRTI-Based Regimens

Preferred	**EFV* + 2 NRTIs: children aged ≥3 years** **NVP + 2 NRTIs: children aged <3 years or requiring liquid formulation**
Alternative	**NVP** + 2 NRTIs (aged ≥3 years)**

Available in capsules and tablets. EFV is teratogenic and should not be used during pregnancy or by sexually active girls with childbearing potential.
** Available in liquid formulation. NVP should not be initiated in girls with CD4 counts >250 cells/μL or in boys with CD4 counts >400 cells/μL.

Etravirine not recommended due to lack of pediatric formulation, lack of pediatric pharmacokinetic data, lack of efficacy or safety data in children, and lack of data in antiretroviral-naïve patients

Initial Treatment:
PI-Based Regimens

- **Preferred**

  LPV/RTV + 2 NRTIs

- **Alternative**

  ATV + low-dose RTV + 2 NRTIs (children aged ≥6 years)
  FPV + low-dose RTV + 2 NRTIs (children aged ≥6 years)
  NFV + 2 NRTIs (children aged ≥2 years)

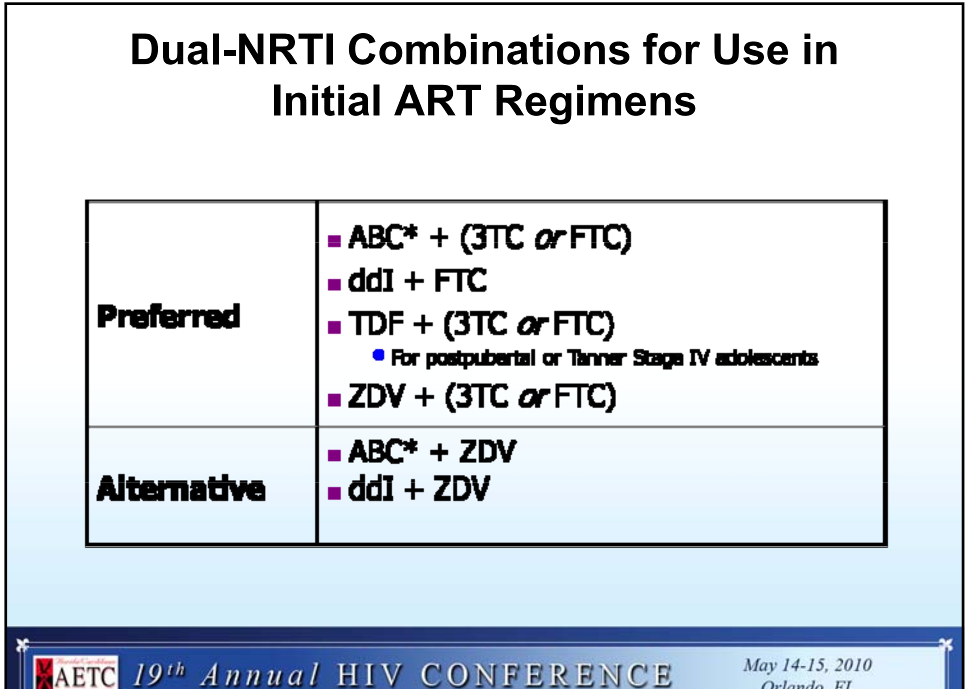
PI Based Regimens contd

- Use in special circumstances:
- Atazanavir unboosted (for treatment-naïve adolescents age >13 years and >39 kg who are unable to tolerate ritonavir) in combination with 2 NRTIs (must be boosted with ritonavir if used with tenofovir)
- Fosamprenavir unboosted (for children age >2 years) in combination with 2 NRTIs

PI Based Regimens contd

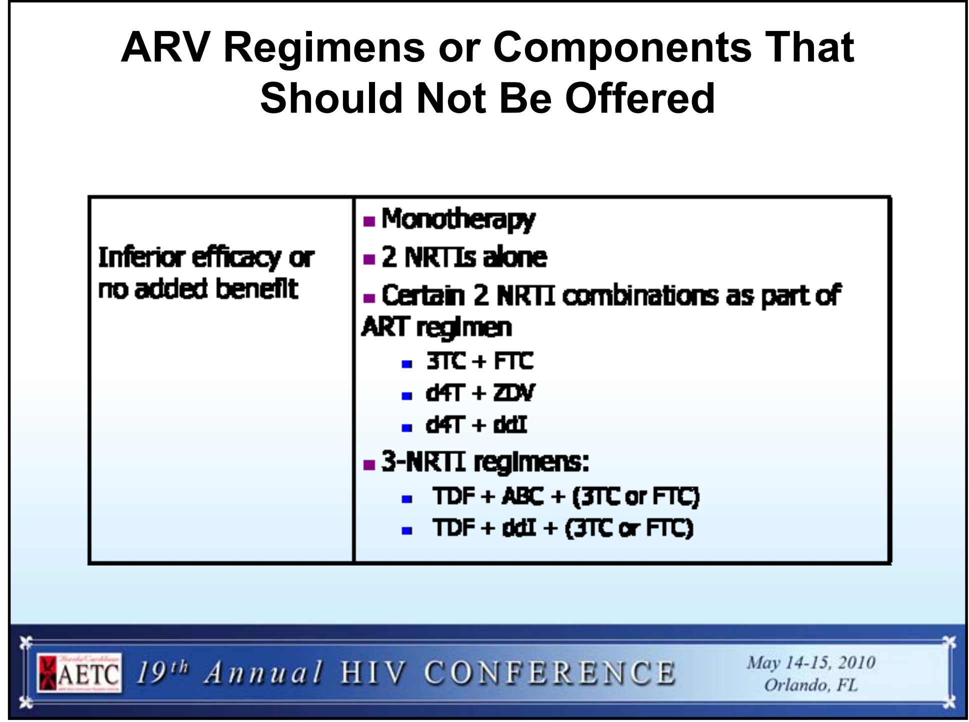
The Working Group does not recommend the following PIs as initial therapy in children because of insufficient data, data related to toxicity or potency, or inconvenient dosing:

- Tipranivir, darunavir, saquinavir, indinavir, and other PIs not in the list above
- Dual (full-dose) PIs
- Full-dose ritonavir or use of ritonavir as the sole PI
- Unboosted atazanavir-containing regimens in children age <13 years and/or <39 kg



Dual-NRTI Combinations for Use in Initial ART Regimens

Preferred	ABC* + (3TC *or* FTC) ddI + FTC TDF + (3TC *or* FTC) • For postpubertal or Tanner Stage IV adolescents ZDV + (3TC *or* FTC)
Alternative	ABC* + ZDV ddI + ZDV



ARV Regimens or Components That Should Not Be Offered

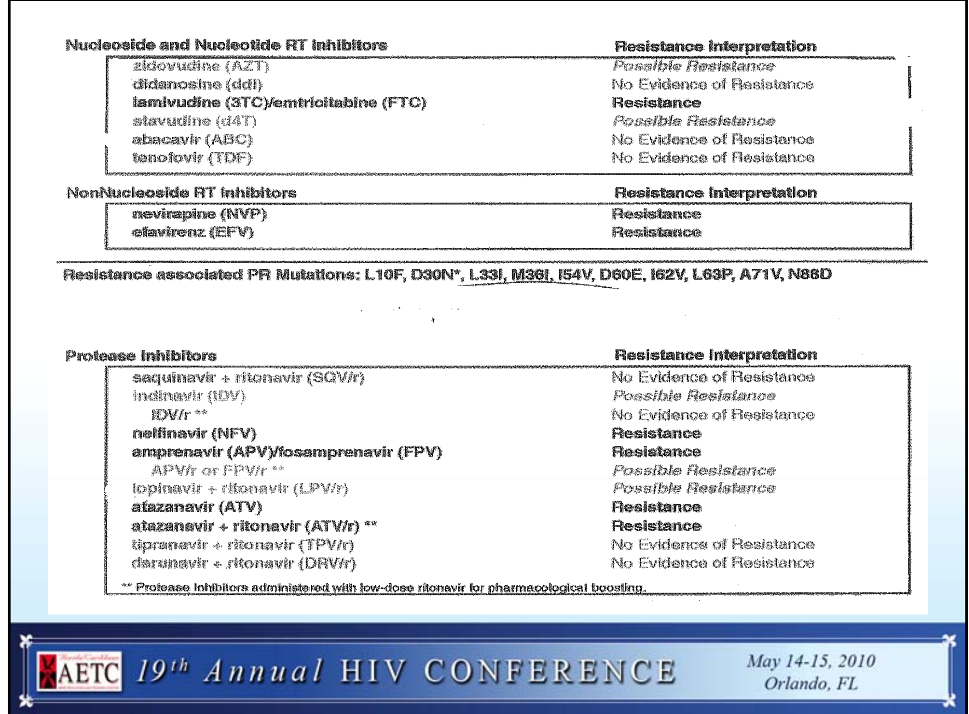
Inferior efficacy or no added benefit	▪ Monotherapy ▪ 2 NRTIs alone ▪ Certain 2 NRTI combinations as part of ART regimen ▪ 3TC + FTC ▪ d4T + ZDV ▪ d4T + ddI ▪ 3-NRTI regimens: ▪ TDF + ABC + (3TC or FTC) ▪ TDF + ddI + (3TC or FTC)

Considerations for Adolescents

- **Tailor ARV regimen to the individual adolescent**
- **Determine appropriate dosage:**
  - Physiologic changes may affect drug pharmacokinetics
  - ARVs usually dosed according to Tanner stage, but drug levels not always predictable
  - Weight- or surface area-based dosages used for children may be too high for adolescents: consult dosing recommendations

Considerations for Adolescents

- **Avoid NVP initiation in adolescent girls with CD4 counts of >250 cells/µL or adolescent boys with CD4 counts of >400 cells/µL**
- **Avoid EFV in girls who may become pregnant by choice or through inconsistent use of birth control**
- **Be aware of drug interactions between oral contraceptives and certain PIs and NNRTIs**
  - Depending on the specific interaction, may lead to failure of the contraceptive or of ART; in some cases, may cause toxicity
  - Efficacy of injectable progestogen contraceptives in women on ARVs is unclear
  - No data on hormonal contraceptive patch or vaginal ring



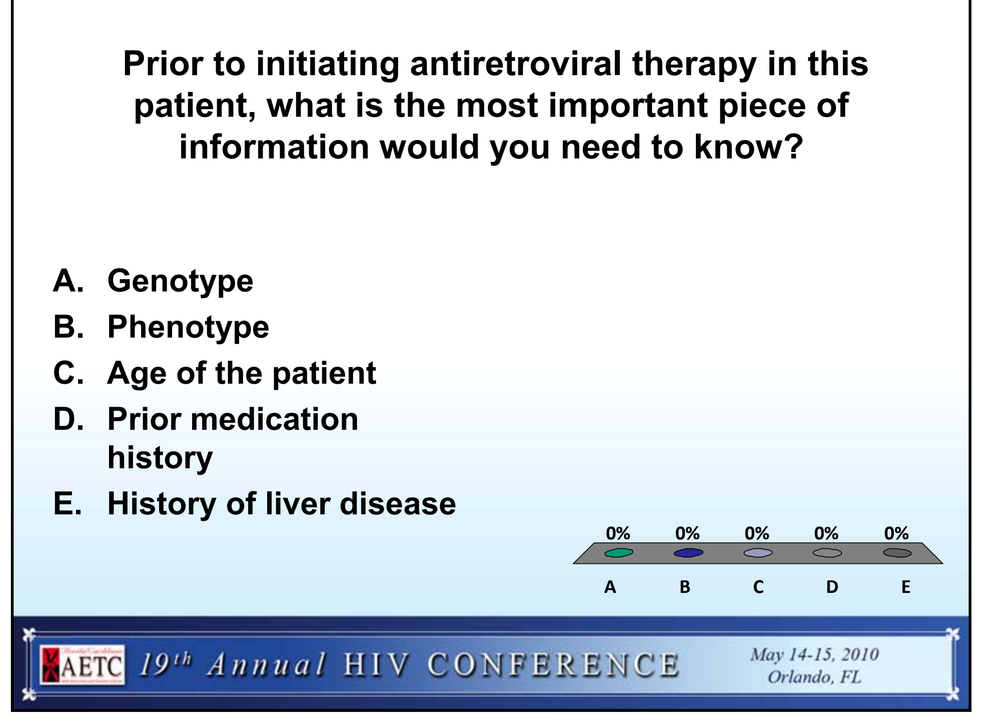
Nucleoside and Nucleotide RT Inhibitors	Resistance Interpretation
zidovudine (AZT)	*Possible Resistance*
didanosine (ddI)	No Evidence of Resistance
lamivudine (3TC)/emtricitabine (FTC)	**Resistance**
stavudine (d4T)	*Possible Resistance*
abacavir (ABC)	No Evidence of Resistance
tenofovir (TDF)	No Evidence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

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

Resistance associated PR Mutations: L10F, D30N*, L33I, M36I, I54V, D60E, I62V, L63P, A71V, N88D

Protease Inhibitors	Resistance Interpretation
saquinavir + ritonavir (SQV/r)	No Evidence of Resistance
indinavir (IDV)	*Possible Resistance*
IDV/r **	No Evidence of Resistance
nelfinavir (NFV)	**Resistance**
amprenavir (APV)/fosamprenavir (FPV)	**Resistance**
APV/r or FPV/r **	*Possible Resistance*
lopinavir + ritonavir (LPV/r)	*Possible Resistance*
atazanavir (ATV)	**Resistance**
atazanavir + ritonavir (ATV/r) **	**Resistance**
tipranavir + ritonavir (TPV/r)	No Evidence of Resistance
darunavir + ritonavir (DRV/r)	No Evidence of Resistance

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


Prior to initiating antiretroviral therapy in this patient, what is the most important piece of information would you need to know?
A. Genotype
B. Phenotype
C. Age of the patient
D. Prior medication history
E. History of liver disease
0%
0%
0%
0%
0%
A
B
C
D
E
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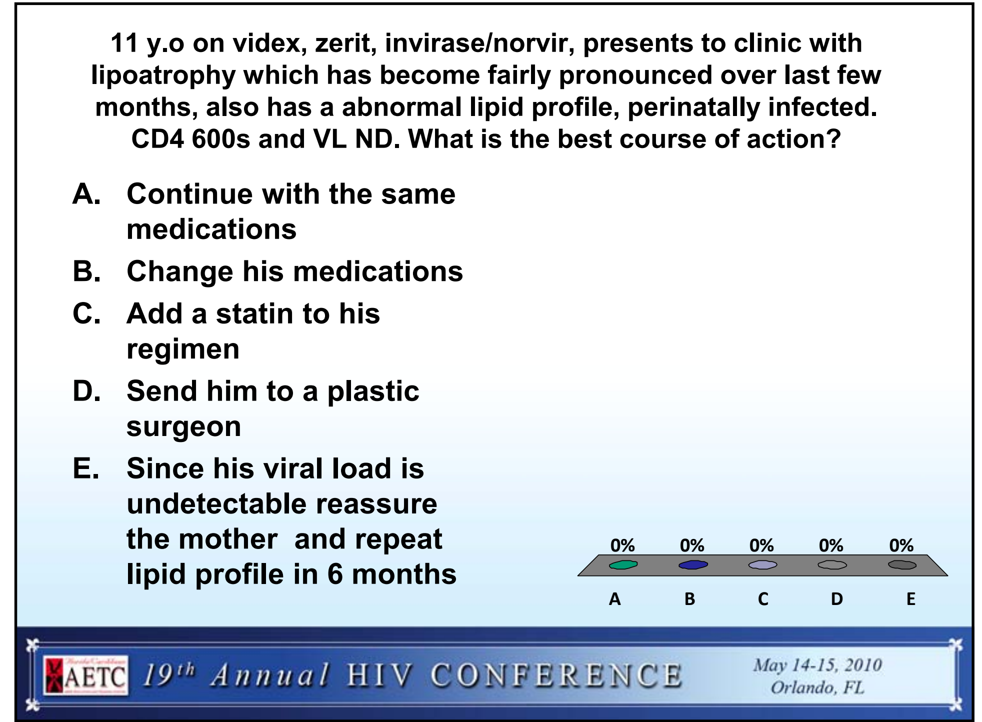
11 y.o on videx, zerit, invirase/norvir, presents to clinic with lipoatrophy which has become fairly pronounced over last few months, also has a abnormal lipid profile, perinatally infected. CD4 600s and VL ND. What is the best course of action?
A. Continue with the same medications
B. Change his medications
C. Add a statin to his regimen
D. Send him to a plastic surgeon
E. Since his viral load is undetectable reassure the mother and repeat lipid profile in 6 months
0%
0%
0%
0%
0%
A
B
C
D
E
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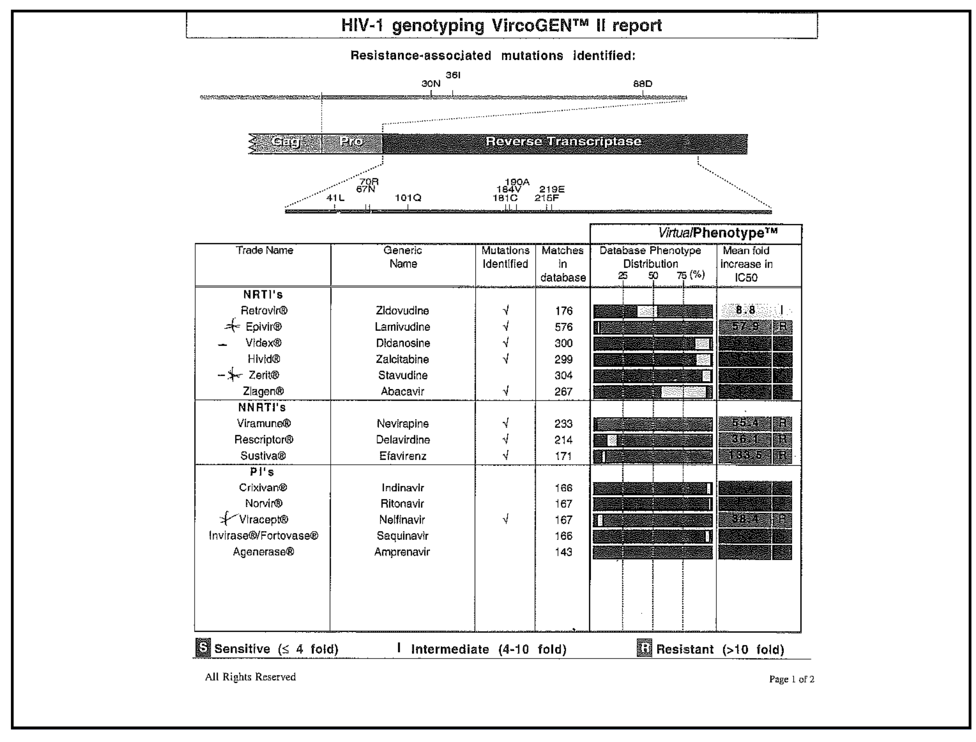

HIV-1 genotyping VircoGEN™ II report

Resistance-associated mutations identified:

30N 36I 88D

Gag Pro Reverse Transcriptase

41L 67N 70R 101Q 181C 184V 190A 215F 219E

Trade Name	Generic Name	Mutations Identified	Matches in database	*Virtual*Phenotype™ Database Phenotype Distribution 25 50 75 (%)	Mean fold increase in IC50	
NRTI's						
Retrovir®	Zidovudine	√	176		8.8	I
Epivir®	Lamivudine	√	576		57.9	R
Videx®	Didanosine	√	300			
Hivid®	Zalcitabine	√	299			
Zerit®	Stavudine		304			
Ziagen®	Abacavir	√	267			
NNRTI's						
Viramune®	Nevirapine	√	233		55.4	R
Rescriptor®	Delavirdine	√	214		36.1	R
Sustiva®	Efavirenz	√	171		133.5	R
PI's						
Crixivan®	Indinavir		166			
Norvir®	Ritonavir		167			
Viracept®	Nelfinavir	√	167		38.4	R
Invirase®/Fortovase®	Saquinavir		166			
Agenerase®	Amprenavir		143			

S Sensitive (≤ 4 fold) I Intermediate (4-10 fold) R Resistant (>10 fold)

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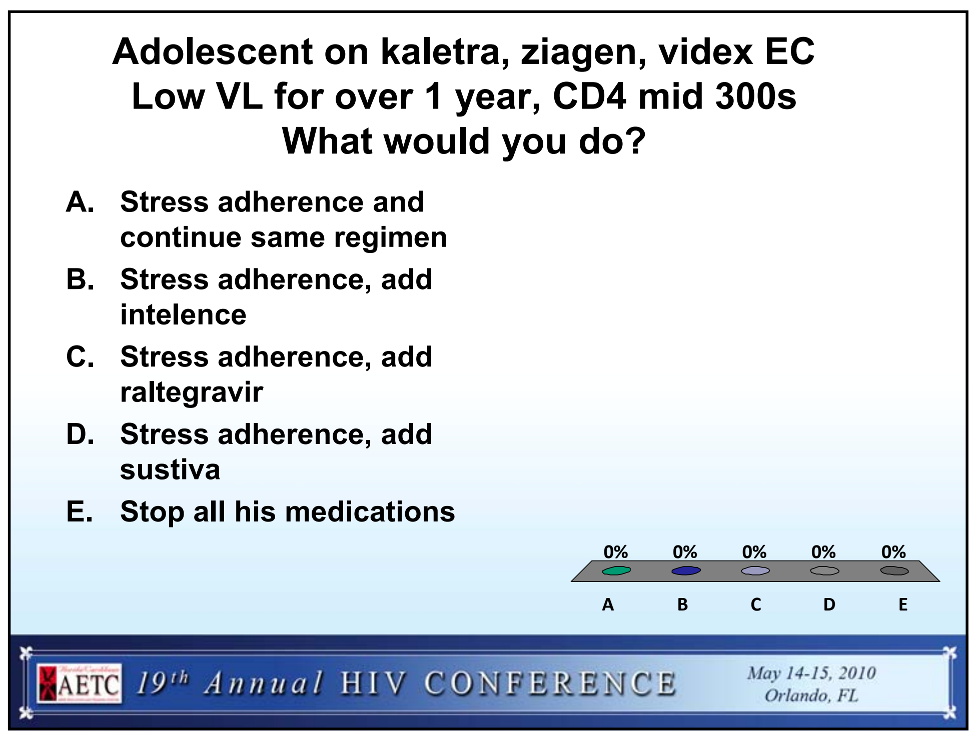

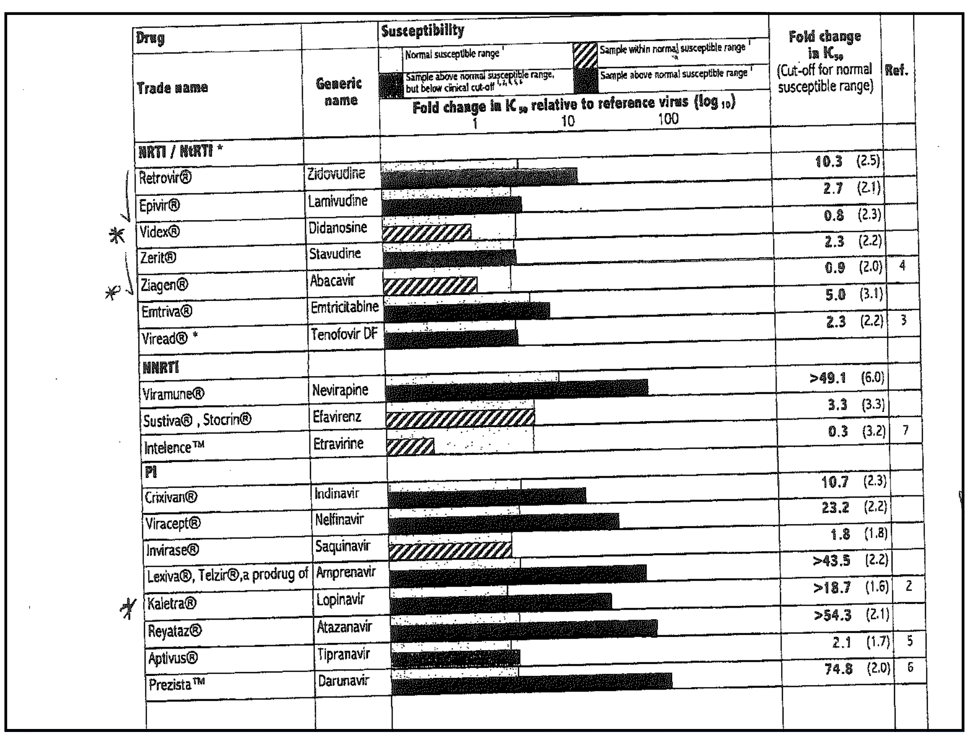

Drug Trade name	Generic name	Susceptibility (Fold change in IC_{50} relative to reference virus (log_{10}))	Fold change in IC_{50} (Cut-off for normal susceptible range)	Ref.
NRTI / NtRTI *				
Retrovir®	Zidovudine		10.3 (2.5)	
Epivir®	Lamivudine		2.7 (2.1)	
Videx®	Didanosine		0.8 (2.3)	
Zerit®	Stavudine		2.3 (2.2)	
Ziagen®	Abacavir		0.9 (2.0)	4
Emtriva®	Emtricitabine		5.0 (3.1)	
Viread® *	Tenofovir DF		2.3 (2.2)	3
NNRTI				
Viramune®	Nevirapine		>49.1 (6.0)	
Sustiva® , Stocrin®	Efavirenz		3.3 (3.3)	
Intelence™	Etravirine		0.3 (3.2)	7
PI				
Crixivan®	Indinavir		10.7 (2.3)	
Viracept®	Nelfinavir		23.2 (2.2)	
Invirase®	Saquinavir		1.8 (1.8)	
Lexiva®, Telzir®,a prodrug of	Amprenavir		>43.5 (2.2)	
Kaletra®	Lopinavir		>18.7 (1.6)	2
Reyataz®	Atazanavir		>54.3 (2.1)	
Aptivus®	Tipranavir		2.1 (1.7)	5
Prezista™	Darunavir		74.8 (2.0)	6

Take Home Points

- Children are not just 'little adults'
- Attention needs to be paid to several factors when designing regimens for children, i.e. age, weight, palatability and availability of liquid formulations, size of pills/capsules, long term side effects, once daily vs twice daily regimens
- While there are several options now available for adults options for younger children are still limited

Selected References

1. Pharmacokinetics, safety and efficacy of darunavir/ritonavir in treatment experienced children and adolescents. Blanche S, Bologna R, Cahn P, Rugina S, et al. AIDS. 2009; 23:2005-13

2. Guidelines for the use of antiretroviral agents in Pediatric HIV infection, 23 February 2009. Available at: http://aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf. Accessed April 29, 2010

3. ARV Therapy in Pediatrics, June 2009. Fl/Caribbean AETC.

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