Are We Over-dosing Antivirals? A Debate

FDA Perspective

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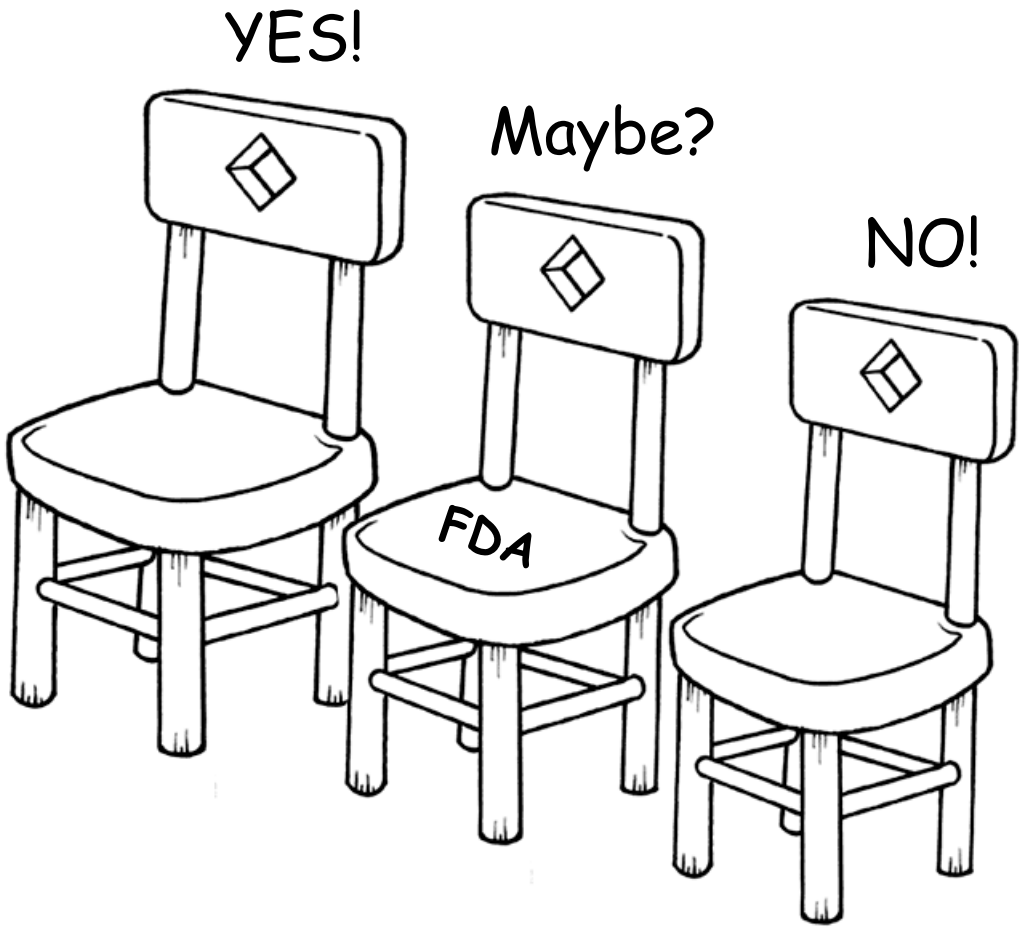

YES!
Maybe?
NO!
FDA

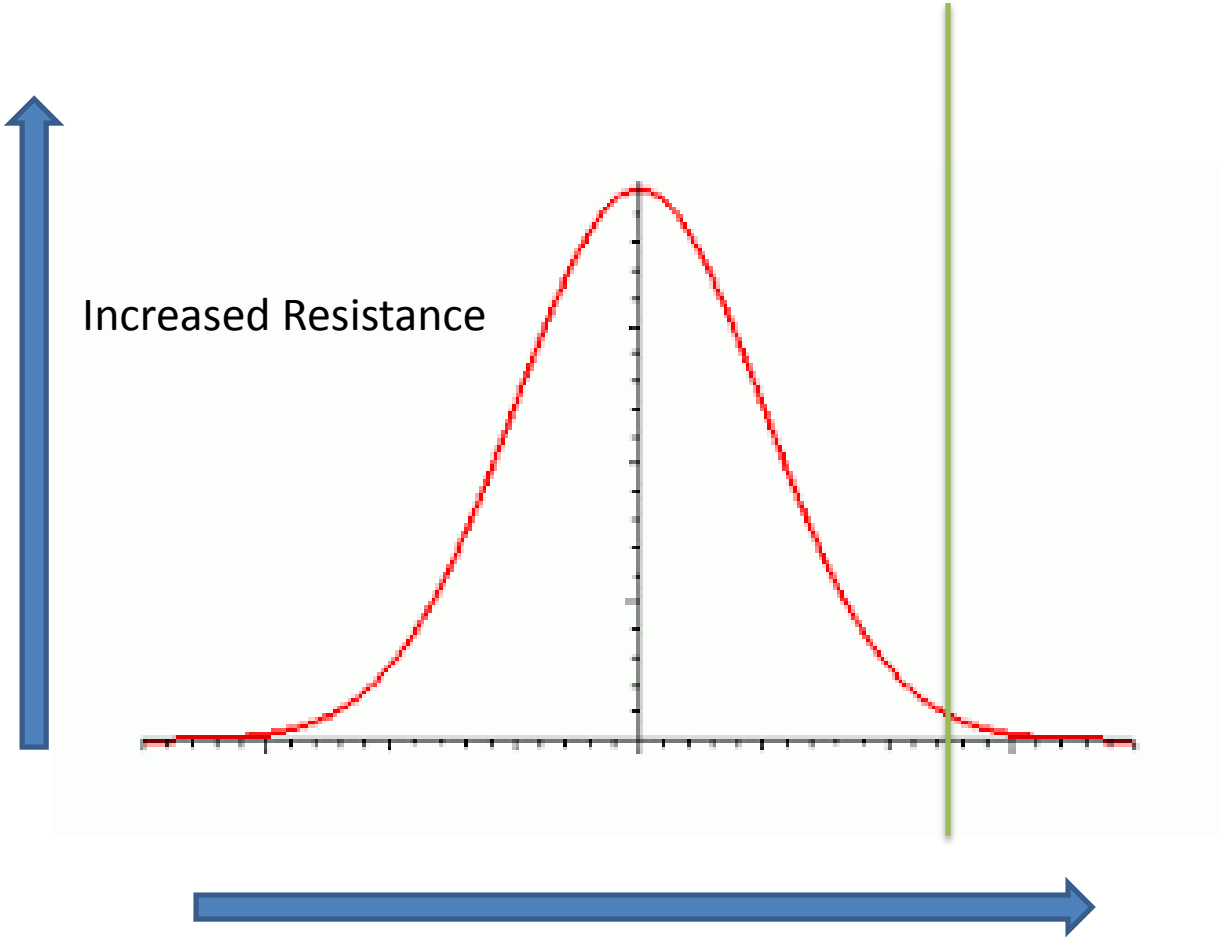
Why Do We Care If the Dose is Too High?

- Increased Adverse Reactions, less tolerable
- Increased or more severe drug-drug interactions?
- Increased Cost (not so much for U.S. market)
- “Optimizing Dose” for individuals where there is variable exposures
- But if #1, 2, and 3 are not issues, isn’t it better to have one size fits all? Avoids additional testing or consideration of baseline factors.

Antiviral Drug Development

- FDA bias was/is toward studying higher doses in phase 3 and for use of more drugs in a combination regimen (for chronic viruses). Why?
- Avoiding development of resistance and loss of future treatment options.
- Even during phase 2, we try to avoid "suboptimal" doses
- Drug-drug interactions may decrease exposures for some-- risking resistance

HIV Drug Resistance vs. Exposure

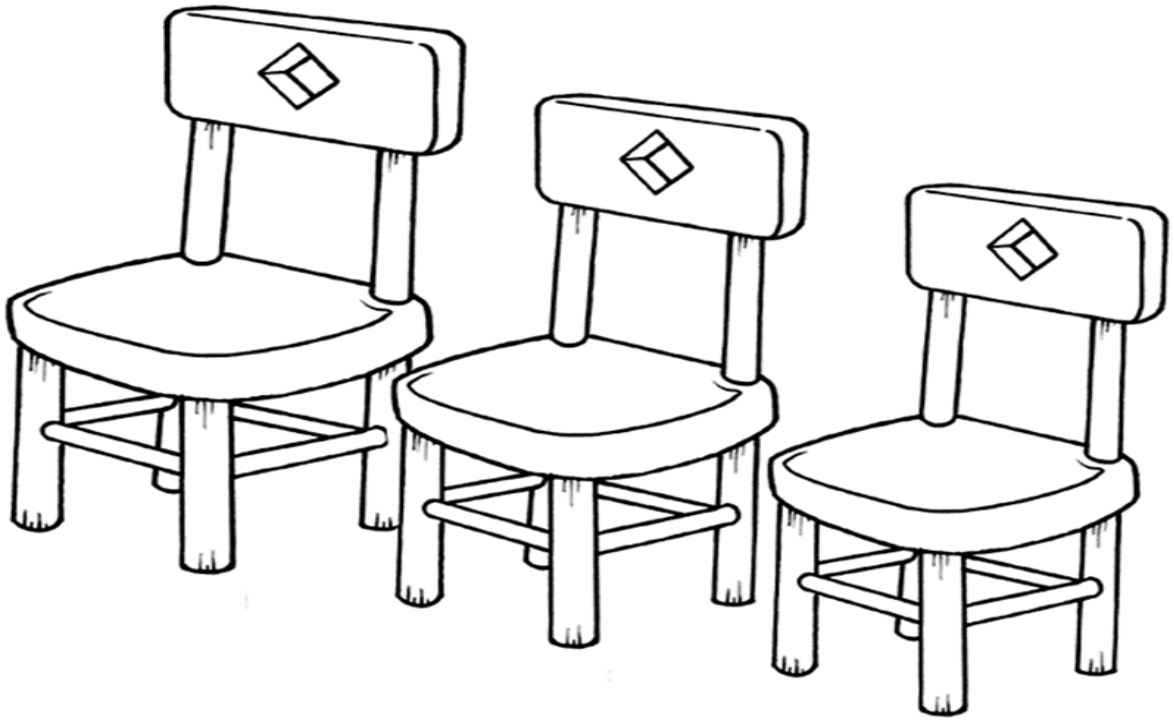


HIV Track Record: Approved Dose
(initial)

Too High
Zidovudine
Efavirenz
Lopinavir/rtv?

Middle Ground
Darunavir/ritonavir
Dolutegravir

Too Low
Rilpivirine
Saquinavir
Other Unboosted PIs



Efavirenz Dose-Finding DMP 266-005

EFV vs Placebo combined with ZDV+3TC. Week 16.

	Placebo	200 mg	400 mg	600 mg
HIV-RNA <400 copies	12/33 (36%)	29/36 (81%)	25/34 (74%)	24/34 (71%)
Dizziness	18%	19%	29%	44%

ENCORE1:
Efavirenz: 400 mg vs 600 mg

"The ENCORE1 study establishes that a lower daily dose of EFV (33% reduction) can be given as initial treatment for HIV infection in adults without any loss of antiretroviral efficacy coupled with indications of improved safety and tolerability. These findings provide an opportunity to reduce the unit costs of treatment and care models that are based on efavirenz use."

"A 33% reduction in the active pharmaceutical ingredient would yield a potential cost saving per patient per year of US $21 and 3-year market effect of about $233–336 million."

Lopinavir/Rtv Dose Finding

TRIAL 720: TREATMENT-NAÏVE PATIENTS. HIV-RNA < 50 copies/mL (%)

Lop/Rtv + 2 NRTIs	On Treatment	ITT
200/100 mg	16/16 (100%)	16/16 (100%)
400/100 mg (group 1)	9/14 (64%)	9/16 (56%)
400/100 mg (group 2)	30/32 (94%)	30/35 (86%)

TRIAL 957: PI-EXPERIENCED. HIV-RNA < 400 copies/mL (%)

Lop/Rtv + EFV + RTIs	On Treatment	ITT
400/100 mg	20/25 (80%)	20/29 (69%)
533/133 mg	23/25 (92%)	23/28 (82%)

Rilpivirine (RPV)
C-204 Dose-Ranging Trial

	RPV 25 mg N=93	RPV 75 mg N=95	RPV 150 mg N=81	EFV 600 mg N=99
% VL < 50 copies	81%	80%	77%	81%
DC due to AE	6%	5%	10%	6%
DC other reasons	4%	8%	7%	8%

Rilpivirine (phase 3 results) Baseline HIV-RNA >100,000

	RPV (N=686)	EFV (N=682)
BL ≤ 100,000 copies % Success	89%	83%
BL > 100,000 copies % Success	75%	77%
BL ≤ 100,000 copies % VL > 50 copies	5%	5%
BL > 100,000 copies % VL > 50 copies	22%	13%

Overdosing vs. Too Many Drugs in a Regimen

Fixed Dose Combination CFR 300.50

- Flexibility in interpretation
- Factorial Designs not always done and not "required." Can use nonclinical data or other early clinical data to support the contribution of drug components in a regimen
- Some combinations may be "overkill" for certain genotype/subtypes or subpopulations
- To define the optimal dose/regimen for every population may be cost prohibitive or unacceptably slow down drug development

HCV: Viekira Pak + Ribavirin

- Recommended regimen for Genotype 1b:
- Non-cirrhotics: Viekira Pak for 12 weeks (SVR 100%)
- Cirrhotics: Viekira Pak + RBV for 12 weeks (SVR 99%)
- Is RBV necessary for cirrhosis 1b?
  Not sure but we only have sufficient data for Viekira Pak + RBV in cirrhotics so labeled for use with RBV

Summary Points

- FDA “bias” toward higher doses arose from desire to prevent resistance
- Current HIV-RNA “efficacy endpoint” measures both virologic failure and tolerability failure (NC=F)
- Resistance (from failure) is a permanent AE in HIV; tolerability issues are largely reversible
- For HCV drugs there appears to be incentive to maximizing the most compact/tolerable regimen to gain market share


TAKE
PILLS
AND
JUST BE
HAPPY