PI remain important option for first line

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Clinical decision making

1) Expertise of the treating phycisian
2) Teaching and training of the phycisian
3) Available evidence

Clinical decision making

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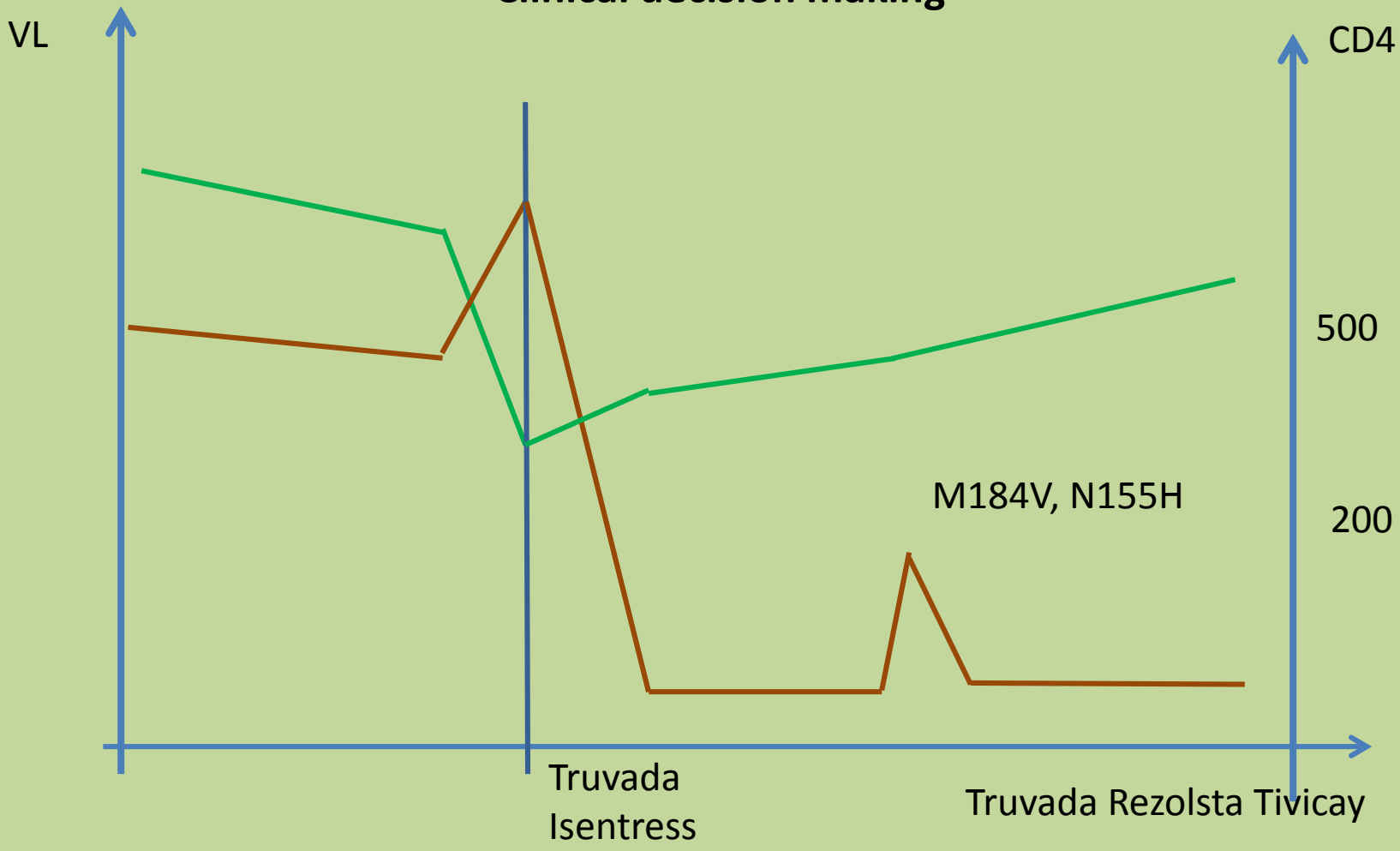
Clinical decision making



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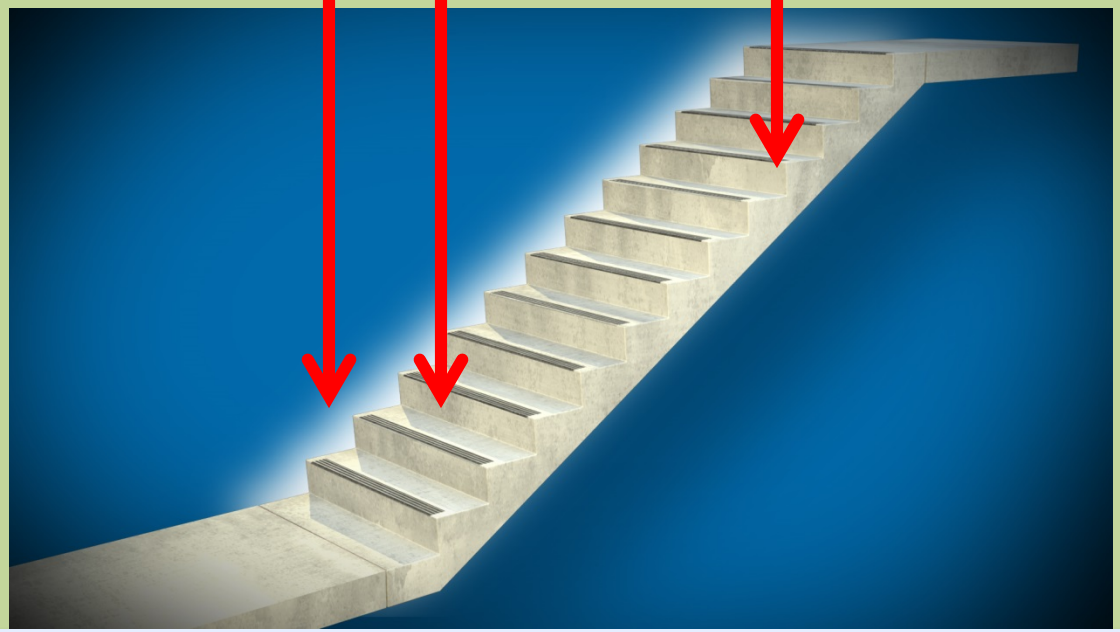
Clinical decision making

K103 N
M184V

G140S
Q148H

Whole list



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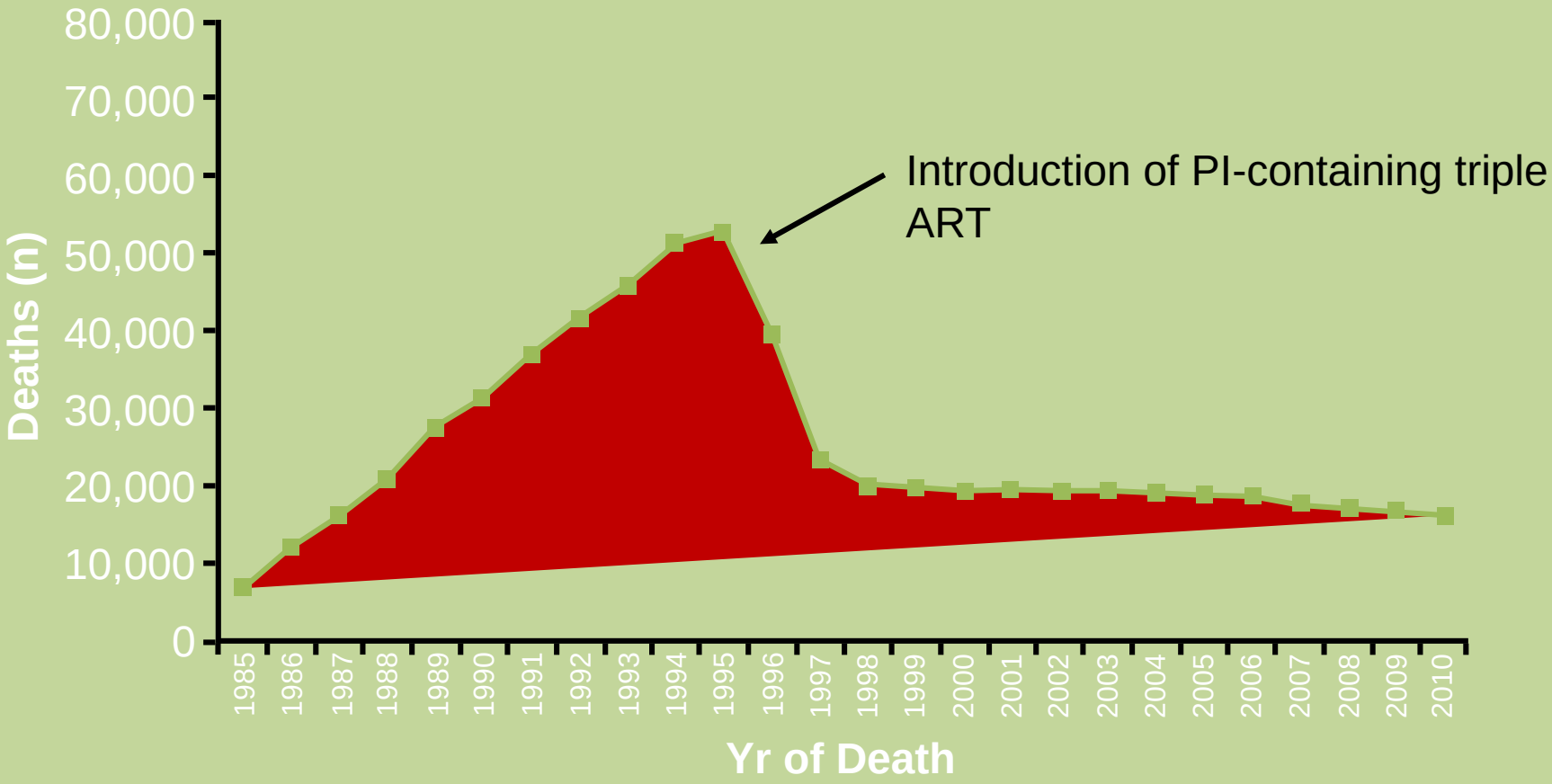
AIDS-Related Mortality and Advent of PIs



CDC.gov. Epidemiology of HIV infection.

Milestones in the Evolution of the PI Class

Many pills per day
Multiple doses necessary
High toxicity

SQV
RTV
IDV

Improved tolerability
Some boosted

SQV/RTV **APV**
IDV/RTV **NFV**

ATV
ATV/RTV
DRV/RTV

1 pill per day (+ RTV & NRTIs)
Boosting gold standard
Manageable toxicity

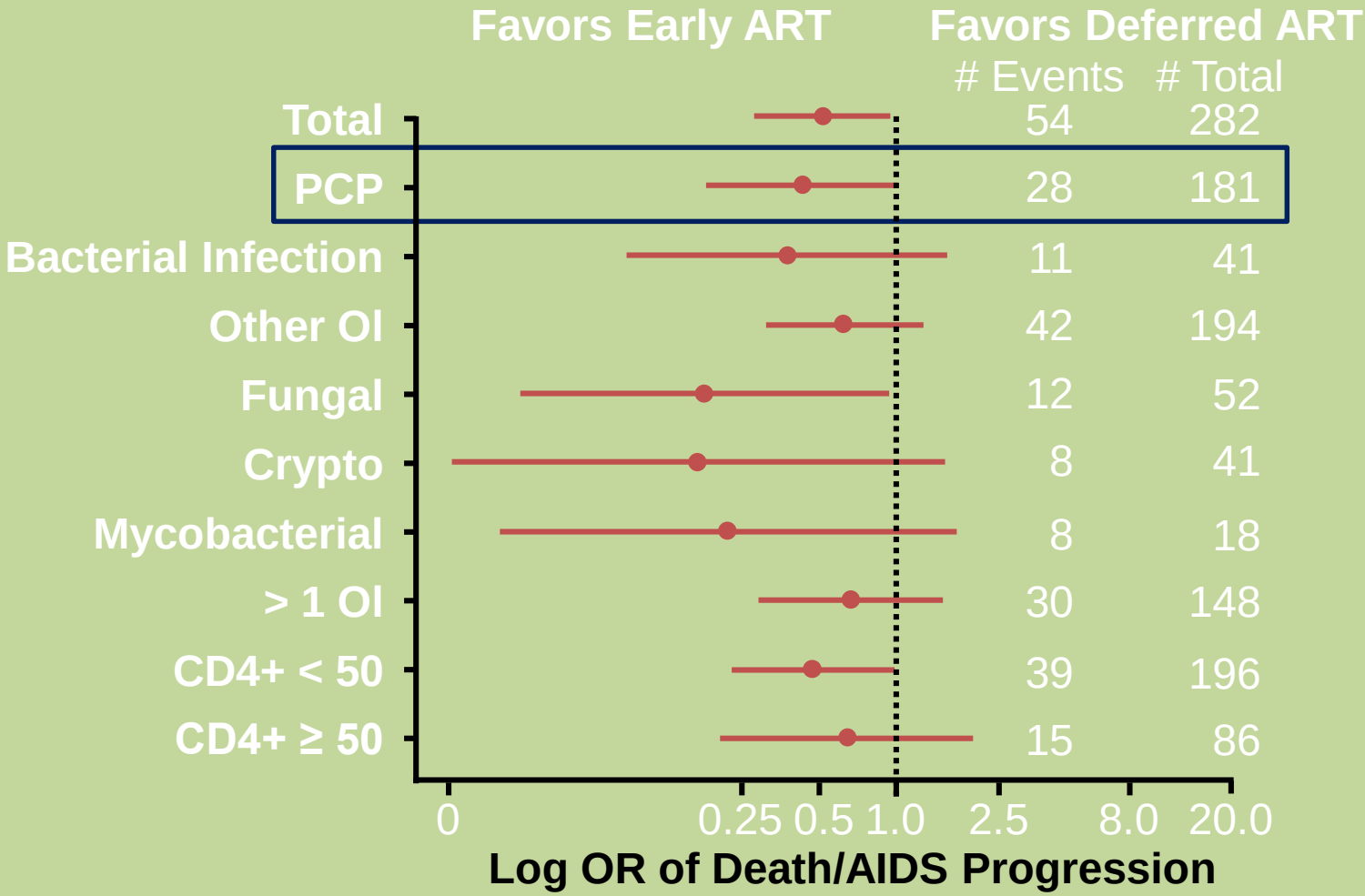
More coformulations
Single-tablet regimens

ATV/COBI
DRV/COBI
DRV/COBI/TAF/FTC

Once-daily dosing
Coformulation
Some treatment-limiting toxicity

FPV/RTV
LPV/RTV

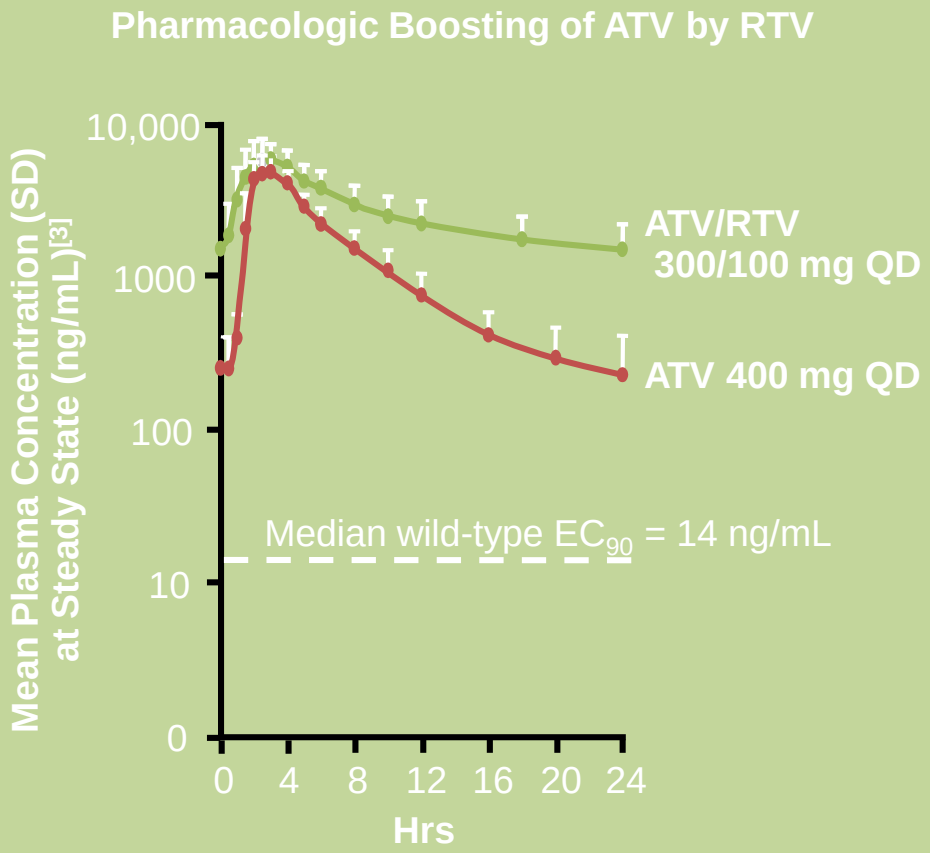
ACTG 5164: Immediate vs Deferred ART for Acute OI



Zolopa AR, et al. PLoS One. 2009;4:e5575.

Ritonavir-Boosted PIs

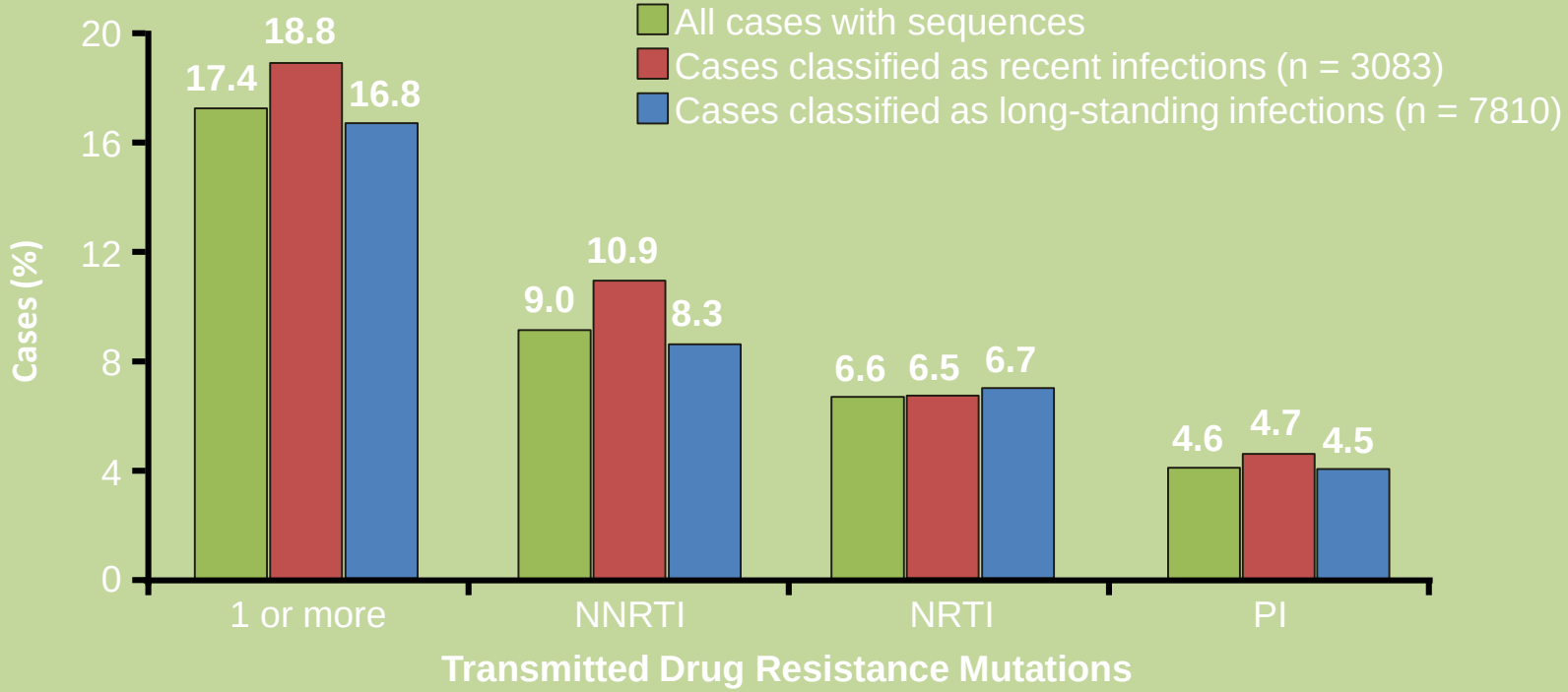
- PIs traditionally coupled with RTV (100-400 mg QD) as a pharmacologic booster
- RTV inhibits CYP3A4 in the liver, increasing PI exposure and half-life[1]
- Boosting allows less frequent PI administration and lower daily dose
- RTV associated with diarrhea and nausea, increased lipids, many drug–drug interactions[2]



1. Merry C, et al. AIDS 1997;11:F29-F33. 2. Ritonavir [package insert]. 3. Atazanavir [package insert].

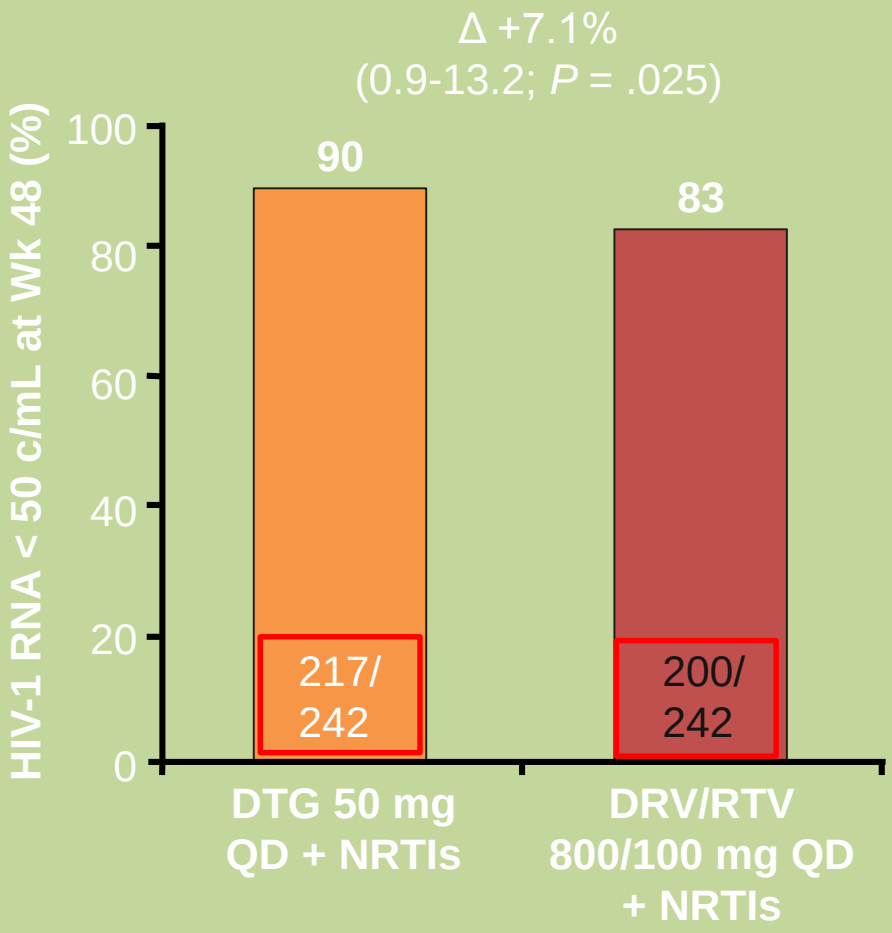
Transmitted HIV Drug Resistance in MSM in 11 Jurisdictions, 2008-2011

- Genotypic analysis of pol sequences of samples from 10,894 newly diagnosed MSM pts in CDC National HIV-1 Surveillance System



Bañez Ocfemia MC, et al. CROI 2014. Abstract 579.

FLAMINGO: DTG vs DRV/RTV + 2 NRTIs in Naive Patients at Wk 48



- DTG superior to DRV/RTV at Wk 48 primary efficacy endpoint
  - Efficacy results better in DTG arm among pts with BL VL > 100K
- VF < 1% (n = 2) in each arm at Wk 48
  - No pts with resistance in either arm at Wk 48
- Treatment-related study d/c: 2% in DTG arm vs 4% in DRV/RTV arm
- Same CD4+ cell count increase at Wk 48: +210 cells/mm^3 in each arm
- Mean increase in fasting LDL-C at Wk 48 significantly lower in DTG arm than DRV/RTV arm (P < .0001)

Clotet B, et al. Lancet. 2014;[Epub ahead of print].

DRV/RTV Adverse Events Summary

- DRV/RTV vs DTG
  - More diarrhea with DRV/RTV; more headache with DTG
  - Small, rapid increase in serum creatinine in first 4 wks of treatment with DTG related to inhibition of tubular secretion of creatinine by DTG

1. Mills A, et al. AIDS. 2009;23:1679-1688. 2. Clotet B, et al. Lancet. 2014;[Epub ahead of print].

abstract

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abstract
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Unexpectedly High Rate of Intolerance for Dolutegravir in Real Life Setting

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results

	total (N=387)		naives(N=65)		non-naives (N=322)	
median age (IQR)	48		46	(22)	48	(13)
female	44	11,4%	8	12,3%	36	11,2%
dutch origin	136	35,1%	28	43,1%	108	33,5%
median CD4/mm3 (IQR)	650		530	(395)	655	(345)
median DGV days (IQR)	220		196	(147)	221	(148)
DGV separate..	156		15		141	
DGV in STR..	231		50		181	

DGV stopped	62	16,0%	13	20,0%	49	15,2%
median DGV days (IQR)	78		81	(71)	75	(99)
female	5	11,4%	3	37,5%	2	5,6%
DGV separate	24	15,4%	1	6,7%	23	16,3%
DGV in STR	38	16,6%	12	24,0%	26	14,4%

reason for interruption

other than toxicity*	6	9,7%	1	7,7%	5	10,2%
toxicity	56	90,3%	12	92,3%	44	89,8%
sleeping..	19	31,3%	5	38,5%	14	28,6%
gastro-intestinal..	18	29,5%	4	30,8%	14	28,6%
neuro-psychiatric..	12	19,7%	3	23,1%	9	18,4%
paresthesia..	6	9,7%	0	0,0%	6	12,2%
headache..	8	12,9%	0	0,0%	8	16,3%
fatigue..	9	14,6%	1	7,7%	8	16,3%
allergy..	1	1,7%	1	7,7%	0	0,0%
other..	5	8,2%	1	7,7%	4	8,2%

*LTFU, HBV protection, insurance, induction, patient request, interaction

What to Start: Initial Combination Regimens for the Antiretroviral-Naive Patient (Last updated January 28, 2016; last reviewed January 28, 2016)

On November 18, 2015, the U.S. Department of Health and Human Services' Panel on Antiretroviral Guidelines for Adults and Adolescents issued a statement regarding the inclusion of elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine as a Recommended regimen for patients with pre-antiretroviral therapy CrCl ≥30 mL/min. An updated What to Start section with discussion regarding this regimen will be available in the next update of the Guidelines.

Panel's Recommendations

- An antiretroviral regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors in combination with a third active antiretroviral drug from one of three drug classes: an integrase strand transfer inhibitor, a non-nucleoside reverse transcriptase inhibitor, or a protease inhibitor with a pharmacokinetic enhancer (cobicistat or ritonavir).
- The Panel classifies the following regimens as Recommended regimens for antiretroviral-naive patients:

  Integrase Strand Transfer Inhibitor-Based Regimens:

  - Dolutegravir/abacavir/lamivudine[a]—**only** for patients who are HLA-B*5701 negative **(AI)**
  - Dolutegravir plus tenofovir disoproxil fumarate/emtricitabine[a] **(AI)**
  - Elvitegravir/cobicistat/tenofovir alafenamide/emtricitabine—**only** for patients with pre-antiretroviral therapy CrCl ≥30 mL/min **(AI)**
  - Elvitegravir/cobicistat/tenofovir disoproxil fumarate/emtricitabine—**only** for patients with pre-antiretroviral therapy CrCl >70 mL/min **(AI)**
  - Raltegravir plus tenofovir/emtricitabine[a] **(AI)**

  Protease Inhibitor-Based Regimen:

  - Darunavir/ritonavir plus tenofovir disoproxil fumarate/emtricitabine[a] **(AI)**
  - On the basis of individual patient characteristics and needs, an Alternative regimen or, less frequently, an Other regimen may in some instances be the optimal regimen for a patient. A list of Alternative and Other regimens can be found in Table 6.
  - Given the large number of excellent options for initial therapy, selection of a regimen for a particular patient should be guided by

Conclusion

PI can be used in first line based on:

- Present in the most guidelines
- Long term confidence with respect to potency
- Long term confidence with respect to safety
- High genetic barrier
- Now available in combination with cobi and in the future even in STR with TAF
- High IQ
- Treatment of acute seroconverters (test and treat)
- Pregnancy