NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Dolutegravir (Tivicay): A Next Generation Integrase Inhibitor

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Dolutegravir (DTG, Tivicay)

- Clinical Trial Data and Resistance
- Prescribing Information
- Drug Interactions

Clinical Trial Data and Resistance

Dolutegravir Phase 3 Studies

Study	Treatment History	Comparison	Response Rates & Key Results
SPRING-2	Naïve	Dolutegravir QD vs. Raltegravir	• Non-inferior (88% vs. 85%) • No dolutegravir resistance • Similar safety
SINGLE	Naïve	Dolutegravir QD vs. Efavirenz	• Superior (88% vs. 81%) • No dolutegravir resistance • Fewer discontinuations
SAILING	≥2-class ARV resistance	Dolutegravir QD vs. Raltegravir	• Superior (71% vs. 64%) • Less virological failure and resistance
VIKING-3	Integrase resistance	Single-arm, Dolutegravir BID	• 64% virological suppression

Sources: 1) Raffi F et al. Lancet 2013;381:735-43. 2) Walmsley S. ICAAC 2012. Abstract H556b. 3) Cahn P et al. Lancet 2013; 382: 700–08. 4) Nichols G et al. IAS 2013.

SAILING: Dolutegravir vs. Raltegravir in Treatment-Experienced Individuals

Study Design

Protocol

- Randomized, double-blind, double-dummy, phase 3 study
- HIV-infected adults with HIV RNA ≥400 copies x2 or ≥1,000 copies x1, plus resistance to at least 2 ARV classes, plus at least 1-2 active drugs

Dolutegravir 50 mg QD + OBT + Placebo
(n = 354)

Raltegravir 400 mg BID + OBT + Placebo
(n = 361)

Key Results:

- Week 48 % with VL <50 favored dolutegravir: 71% vs. 64% (P=0.030)
- Difference greatest in those with high viral loads or not using boosted darunavir
- Fewer virological failures and emergent resistance mutations in dolutegravir arm
- Adverse events similar; small increases in serum Cr seen in dolutegravir arm

Source: Cahn P et al. Lancet 2013; 382: 700–08.

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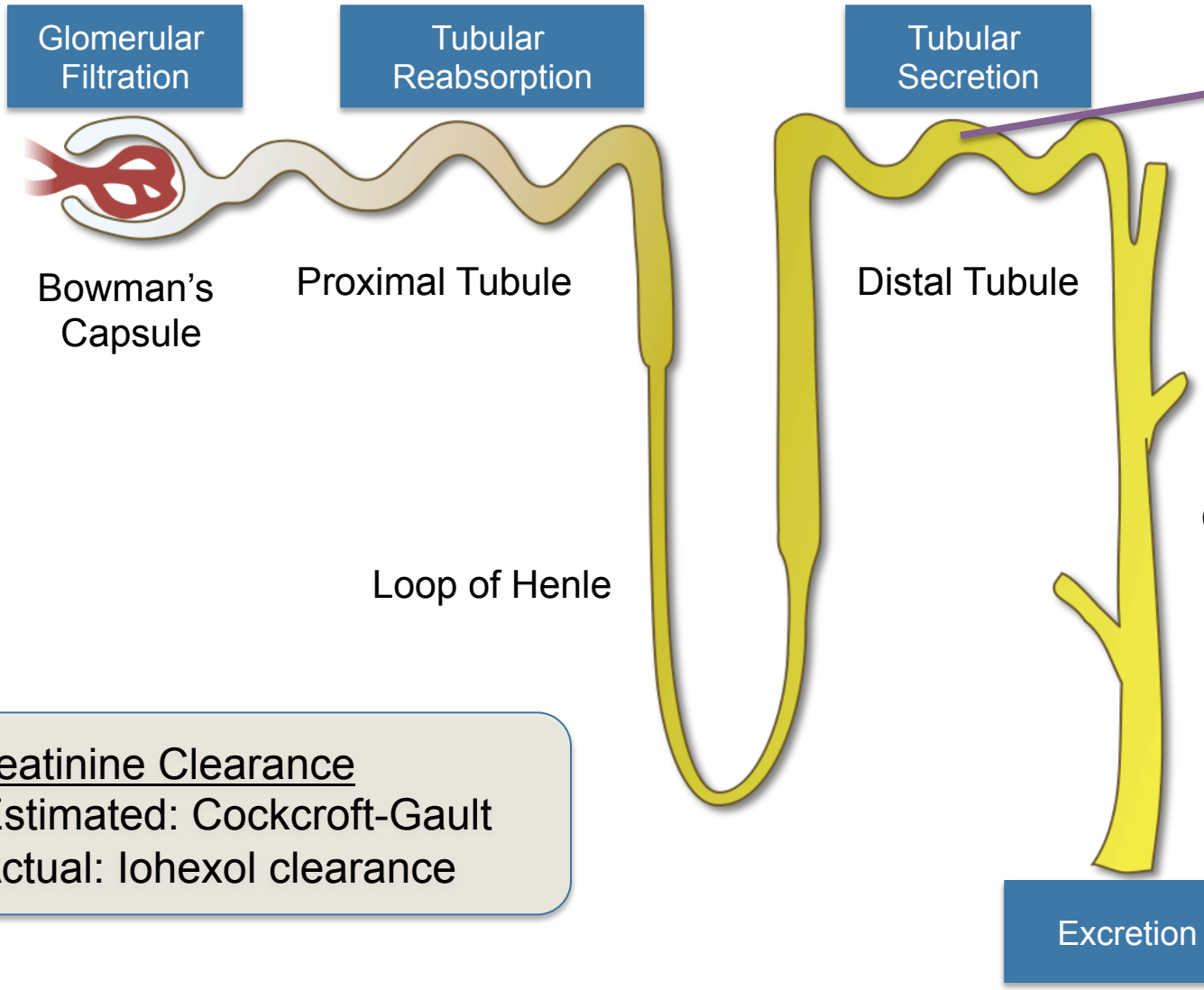
Urine Formation



Creatinine Clearance
- Estimated: Cockcroft-Gault
- Actual: Iohexol clearance

VIKING-3: Dolutegravir in Treatment-Experienced Individuals with Integrase Resistance

Study Design

Protocol

- HIV-infected adults with VL ≥500 copies
- Resistance to raltegravir or elvitegravir, plus resistance to at least 2 additional ARV classes

→ **Dolutegravir 50 mg BID + Failing Regimen**

Functional monotherapy phase (7 days)

→ **Dolutegravir 50 mg BID + OBT**

Day 8 →

Key Results:

- Day 8 mean VL change from baseline: -1.43 log copies
- % with VL <50 copies at 24 weeks: 64%
- 4% discontinued due to adverse events

Sources: 1) ViiV Healthcare Press release. Nov 2012. 2) Nichols G et al. IAS 2013. 3) http://www.viivhealthcare.com/media/58599/us_tivicay.pdf

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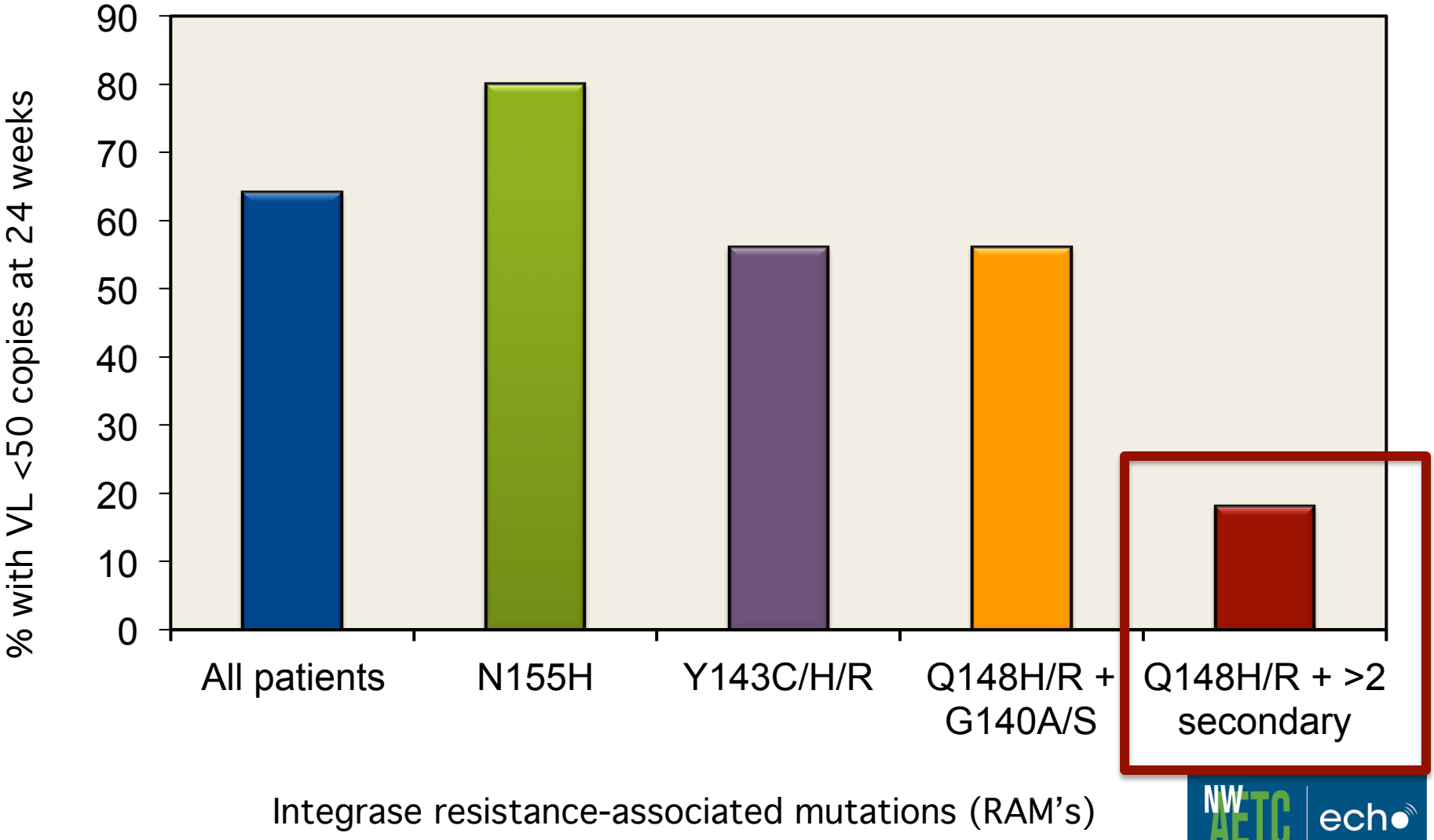
VIKING-3: Dolutegravir 24-week response by baseline integrase RAM



Dolutegravir Response

- Multivariate analysis identified two factors highly associated with decreased response to dolutegravir:
  1) **Q148 + ≥2 secondary mutations**
  2) **Higher baseline fold change**
- Lower response when ≥3 of the following integrase mutations present: L74I/M, E138A/D/K/T, G140A/S, Y143H/R, Q148H/R, E157Q, G163E/K/Q/R/S, G193E/R

Review of Integrase Resistance

Raltegravir	Elvitegravir	Dolutegravir
• N155H • Q148H/R/K • Y143R/H/C	• N155H • Q148H/R/K • E92Q	• Q148 + secondary mutations (G140A/S, E138E/K, etc)

Prescribing Information and Drug Interactions

Prescribing Information

- 50 mg tabs
  - QD if treatment-naïve or integrase-naïve
  - BID if integrase resistance (confirmed or suspected)
  - BID with potent CYP3A4/UGT1A1 inducers (efavirenz, tipranavir/ritonavir, fosamprenavir/ritonavir, rifampin)
- With or without food
- Most common SE's: diarrhea, nausea, headache, insomnia

Sources: 1) http://www.viivhealthcare.com/media/58599/us_tivicay.pdf. 2) http://aidsinfo.nih.gov/drugs/509/dolutegravir/0/patient

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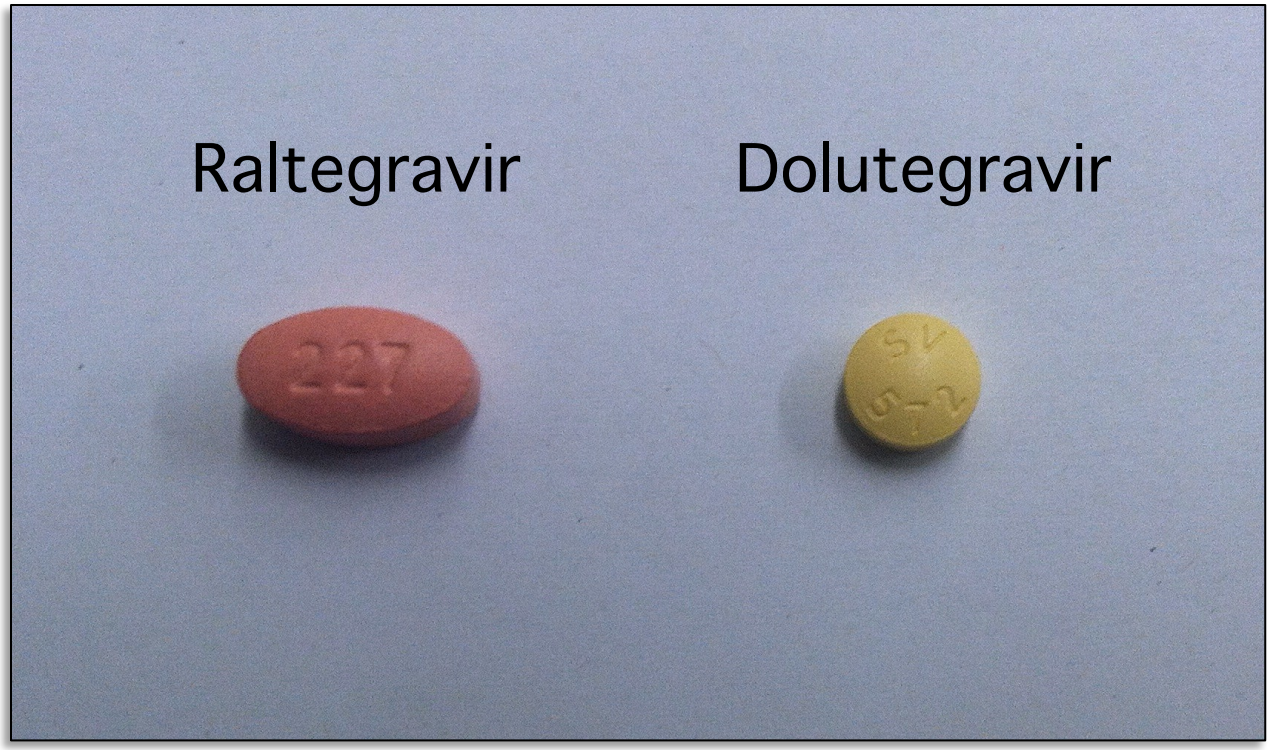
Dolutegravir Tablets



Drug Interactions: ARV's

ARV	Interaction	Recommendation
Efavirenz, boosted fosamprenavir or boosted tipranavir	↓Dolutegravir	-Treatment-naïve or integrase-naïve: dolutegravir BID -Integrase resistance: avoid
Nevirapine	↓Dolutegravir	Avoid
Etravirine	↓Dolutegravir	Avoid unless also giving boosted darunavir, boosted atazanavir or boosted lopinavir
Boosted darunavir, boosted lopinavir, rilpivirine	No clinically significant effect	No adjustment needed

Sources: 1) http://www.viivhealthcare.com/media/58599/us_tivicay.pdf. 2) http://aidsinfo.nih.gov/drugs/509/dolutegravir/0/patient

Drug Interactions: Non-ARV's

Medication	Interaction	Recommendation
Oxcarbazepine, phenytoin, phenobarbital, carbamazepine, St. John's Wort	↓Dolutegravir	Avoid
Cation-containing antacids or laxatives (sucralfate, oral Fe, oral Ca) or buffered medications	↓Dolutegravir	Dolutegravir should be administered 2 hours before or 6 hours after
Rifampin	↓Dolutegravir	Dolutegravir BID
Metformin	↑Metformin	Close monitoring, consider metformin dose adjustment
Dofelitide	↑Dofelitide	Avoid
Boceprevir, telaprevir, prednisone, rifabutin, omeprazole	No significant effect	No adjustment needed

Summary

- Dolutegravir is a potent, next-generation integrase inhibitor available for treatment-naïve or experienced patients
- Active against most cases of integrase resistance (exception: Q148 + ≥2 secondary mutations or higher dolutegravir fold-change)
- Once-daily unless integrase resistance or coadministration with a potent CYP inducer
- Overall well-tolerated with high barrier to resistance

Coming Soon…

- FLAMINGO - dolutegravir vs. boosted darunavir in treatment-naïve individuals
- The “Tri Pill” – abacavir-lamivudine-dolutegravir