NORTHWEST AIDS EDUCATION AND TRAINING CENTER

Novel Antiretrovirals: An Update

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Novel Antiretrovirals: An Update

- **Dolutegravir**: Superior to Boosted Darunavir!
- **Tenofovir Alafenamide (TAF)**: Benefits and Drawbacks
- **Long-Acting Agents**: Whats Coming…Hopefully

FLAMINGO Trial: Dolutegravir vs. Boosted Darunavir in Treatment-Naïve Individuals

FLAMINGO: Dolutegravir vs. Darunavir/Ritonavir in Treatment-Naïve Individuals

Study Design

Protocol

- Multicenter, open-label, randomized
- HIV-infected adults, VL >1,000
- Stratified by baseline VL and NRTI's (TDF-FTC or ABC-3TC)
- Primary endpoint: proportion with HIV RNA <50 (snapshot analysis)

Dolutegravir 50 mg QD + 2 NRTI's
(n = 242)

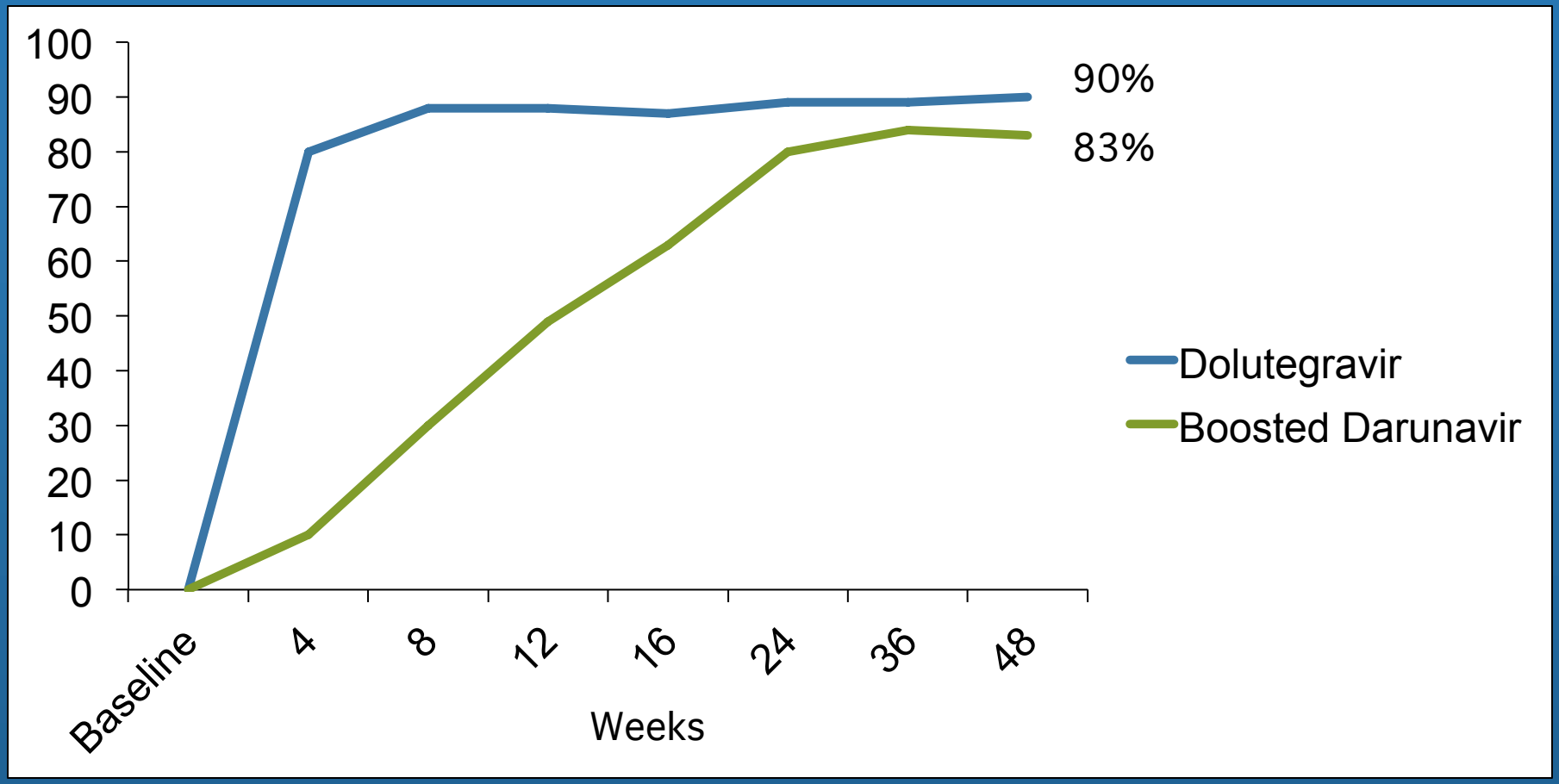
Darunavir 800 mg + Ritonavir 100 mg + 2 NRTI's
(n = 242)

Week 48 Results:

- Similar baseline characteristics (median age 34, 15% women, 28% non-white)
- One third of participants started ABC-3TC, others TDF-FTC
- Week 48 FDA snapshot analysis: dolutegravir superior (90% vs. 83%)

Source: Feinberg J et al. 53rd ICAAC. Sept 10-13, 2013. Denver. Abstract H-1464a.

FLAMINGO Trial 48-Week Results
Proportion with HIV RNA <50 vs. Weeks on Therapy



Source: Feinberg J et al. 53rd ICAAC. Sept 10-13, 2013. Denver. Abstract H-1464a.

Reasons for Superiority of Dolutegravir (DTG)

1) Fewer adverse events & study withdrawals (7% vs. 12%)
   - Less diarrhea, lipid effects with DTG
   - More headache with DTG, similar rates of nausea
2) Fewer virological non-responders at high viral loads
   - Fewer non-responders if baseline HIV RNA >100,000
   - No emergent NRTI, PI, ISTI resistance mutations in either arm
3) Open-label design?
   - Some who got DRV/r may have been hoping for DTG
   - However, dropouts did not occur early

Source: Feinberg J et al. 53rd ICAAC. Sept 10-13, 2013. Denver. Abstract H-1464a.

Summary of Dolutegravir Trials in Treatment-Naïve Individuals

- **FLAMINGO**: *Superior* to boosted darunavir
- **SINGLE**: *Superior* to efavirenz
- **SPRING-2**: Non-inferior to raltegravir

1) Feinberg J et al. 53rd ICAAC. Sept 10-13, 2013. Denver. Abstract H-1464a.
2) Walmsley S et al. 52nd Interscience Conference on Antimicrobial Agents and Chemotherapy; September 9-12, 2012; San Francisco, California. Abstract H-556b.
3) Raffi F et al. Lancet. 2013;381:735-743.

Tenofovir Alafenamide (TAF): Update on Study 102

Tenofovir Alafenamide (TAF)

- What is it? Novel pro-drug of tenofovir (TFV)

- What is the advantage?
  - 10x ↓ plasma levels = less drug to bone, kidneys
  - 5x ↑ intracellular levels = more in PBMC's, lymph tissue, key targets
  - Small dose = easily co-formulated (10 mg w/cobicistat, 25 mg w/out)

Zolopa AR et al, CROI 2013, Abstract 99LB

Tenofovir Alafenamide (TAF): Study 102
48-Week Data from ICAAC 2013

Study Design

Protocol

- Randomized, double-blind, phase 2
- HIV-infected adults with HIV RNA >5,000, CD4 >50, normal GFR, no resistance to TDF, FTC
- Randomized 2:1

EVG-COBI-FTC-TAF
(n = 112)

EVG-COBI-FTC-TDF
(n = 58)

Key Results:

- Subjects: 97% male, 32% non-white, 21% HIV RNA >100,000 copies/mL
- Proportion with VL <50 copies/mL at 48 weeks equivalent (88% vs. 88%)
- Resistance found in 0/3 subjects with VF on TAF, 2/3 subjects with VF on TDF

Sax PE et al. 53rd ICAAC, Denver CO, Sept 10-13, 2013, Abstract H-1464d

Tenofovir Alafenamide (TAF)
48-Week Data from ICAAC 2013: Side Effects

	Change in eGFR (mL/min)	Change in BMD at Hip	Change in BMD at Spine	Nausea	Grade 3/4 Neutropenia	LDL Increases
TAF	**-5.5***	**-0.62%****	**-1.0%****	21%	5%	9%
TDF	-10.0	-2.39%	-3.37%	**12%**	**2%**	**3%**

*Also markers of proximal tubulopathy lower with TAF (retinol binding protein, beta-2-microglobulin)

**In vitro cultures of osteoblasts did not concentrate TAF like PBMC's (no toxicity to osteoblasts with TAF)

1) Sax PE et al. 53rd ICAAC, Denver CO, Sept 10-13, 2013, Abstract H-1464d.
2) Liu Y et al. 53rd ICAAC, Denver CO, Sept 10-13, 2013, Abstract H-664.

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Long-Acting Antiretrovirals: Data from Recent Conferences

Long-Acting Antiretrovirals

- **What's in the works?**
  - GSK-744: a long-acting integrase inhibitor
  - TMC-278 LA: long-acting rilpivirine
- **Data from ICAAC 2013:**
  - Meta-analysis of safety data on GSK-744:
    - 245 subjects in 8 phase I/IIa studies with oral and LA forms
    - Well-tolerated, mostly injection site reactions - primarily grade 1 and not treatment-limiting
    - Supports clinical development

Lou Y et al. 53rd ICAAC. September 10-13, 2013. Denver. Abstract H-672

A Complete Long-Acting ARV Regimen?

- **From IAS 2013:**
  - 40 HIV-uninfected adults received IM or SC GSK-744 + IM TMC-278
  - Overall well-tolerated, mostly injection site reactions
  - Monthly or quarterly dosing achieved adequate plasma levels
- **From ID Week 2013**:
  - Model of cost-effectiveness of long-acting ARV regimen
  - Lifetime cost, cost per QALY:
    - First-line daily oral ART: $400,000
    - First-line LA-ART: $670,000, $6,190,000/QALY
    - Second-line LA-ART: $490,000, $980,000/QALY
    - LA-ART after multiple failures: $420,000, $90,000/QALY

1) Spreen W et al. IAS July 2013, Kuala Lumpur. Abstract WEAB 0103.
2) Ross E et al. IDWeek 2013. October 2-6, 2013. San Francisco. Abstract 78.

Summary

- **Dolutegravir:** superior to boosted darunavir for treatment-naïve individuals (primarily due to fewer SE's)
- **TAF**: less bone and renal toxicity, but possible increased nausea, neutropenia, and lipid effects require further study
- **Long-acting ARV's:** in early-stage development but promising and may be cost-effective for patients with heavy treatment experience and multiple virological failures