Antiretrovirals for Treatment and Prevention: Two Trains on A Collision Course?

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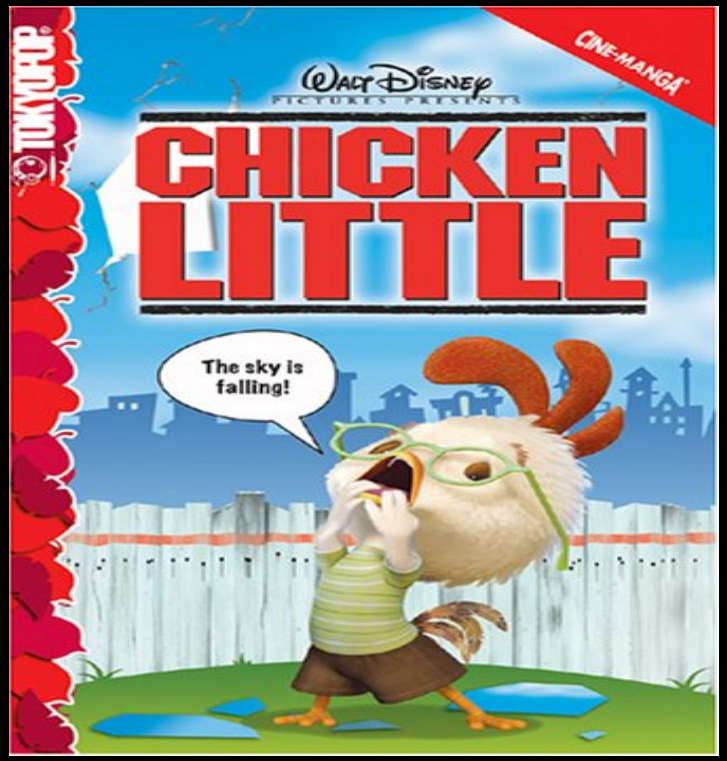
HIV Prevention with Antiretrovirals (ARVs)

- ARV therapy of infected persons (ART)
  - prevent horizontal transmission
  - prevent vertical transmission (maternal ART)
- ARV prevention (ARP) for uninfected persons
  - prevent horizontal transmission (M $\Leftrightarrow$ F; M $\Leftrightarrow$ M)
  - prevent vertical transmission (infant sd NVP)
- Various ARP strategies
  - Mucosal (topical) or systemic (oral, SC, IM) or both
  - Pre- or post-exposure - often both!

There are highly divergent opinions about whether an ARP will promote the spread of HIV-1 drug resistance



There are very few data to support either opinion!

Outline

- Short primer on HIV drug resistance
  - Focus on how to preventing it!
- The two *trains*: ART & ARP
  - Will they collide?
- Some recent insights
  - sdNVP for pMTCT
- Thoughts on minimizing casualties

Lessons Learned from ART

- Resistant variants are rapidly selected by therapy with drugs for which 1 or 2 mutations confer resistance
  - All single and most double mutants exist before therapy
- Incomplete suppression of HIV replication results in accumulation of multiple mutations, greater resistance and broader cross-resistance
  - Replication and mutation are the engine of HIV evolution

Principles of Successful ART

- Cover all pre-existing mutants
  - Single and double drug-resistant mutants
- Suppress new cycles of HIV replication
  - Plasma HIV RNA < 50 copies/ml
- Generally requires 3 potent drugs
  - With non-overlapping resistance mutations

ART MANTRA

Circa 1996

No HIV Replication = No Resistance

The ART Rollout Train

ART Rollout Train

- Approaching 4 million on first-line ART
  - D4T or AZT + 3TC + NVP
  - Suppression ~80% at 1 year
  - 80% not suppressed have drug resistance
    - » 184V, 103N in 75%; 65R in 5-10%; TAMs in 25%
  - **Shift in guidelines to TNV + 3TC + NVP for first-line**
    - » **Expect ↓ in TAMs ↑ in 65R**
- Limited monitoring for HIV drug resistance
  - Not feasible for individual patient management

ART Rollout Train (con't)

- Restricted access to second-line ART
  - % suppression uncertain; 60-70%?
- Few data on transmitted drug resistance
  - WHO and other surveillance programs ongoing
  - Transmitted drug resistance will occur

⇒*Expect prevalence of drug resistance to increase from both acquired and transmitted resistance*

The ARP Train

Drug Resistance from ARP?

- Individuals who are put on ARP with undiagnosed HIV infection will develop resistance
  - Unless ARP is equivalent to ART (practical?)
- Individuals who become infected on ARP will likely develop resistance unless it is stopped promptly
  - Impact of resistance on future response to ART?
- Route of ARP administration may affect resistance
  - Systemic vs. local (both but transmissable)
- Greater efficacy, less resistance

ARP Efficacy vs. Resistance

Number at Risk	Seroincidence	Efficacy of ARP	% Resistant w/ ARP Failure	Individuals with Resistance
100,000	5%	30%	50%	1750
100,000	5%	60%	50%	1000
100,000	5%	90%	50%	250
100,000	5%	95%	50%	125
100,000	5%	99%	50%	25

ARP MANTRA

New Delhi 2008

No HIV Infection = No Resistance!

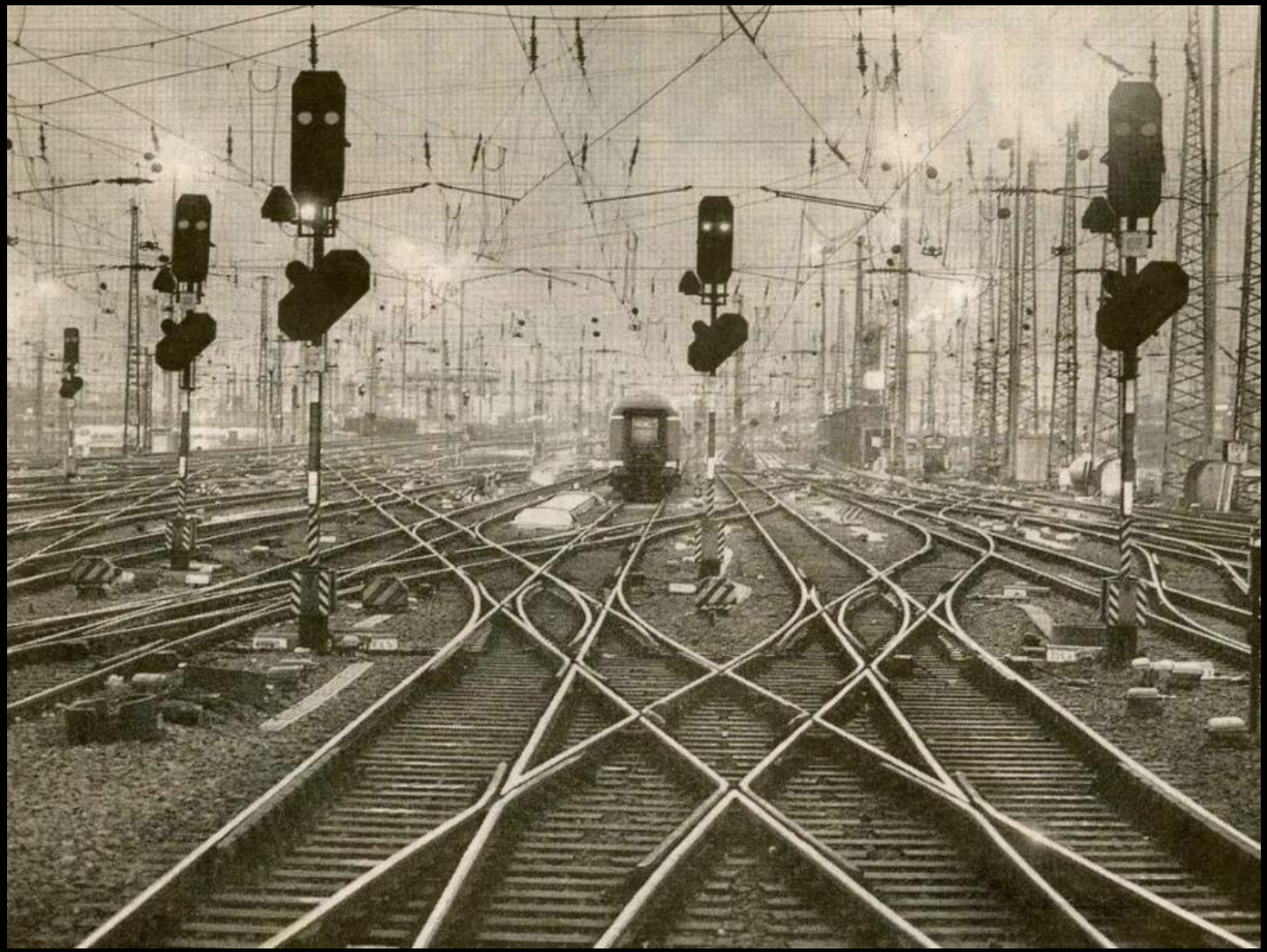
The TNV & TNV/FTC Landscape

	2009	2010	2011	2012	2013
Bangkok IDU (TNV)					
iPrEx (TNV/FTC)					
CAPRISA 004 (TNV gel)					
Partners PrEP (TNV, TNV/FTC)					
FEM-PrEP (TNV/FTC)					
VOICE (TNV gel, TNV,TNV/FTC)					

TNV & FTC Resistance

- TNV Resistance
  - K65R: 3-5 fold
  - K70N/E (rare): 2-3 fold
  - ≥ 3 TAMs: 3-10 fold
- FTC/3TC Resistance
  - M184I: ~20 fold
  - M184V: >100 fold
  - ↑ sensitivity to TNV
- TNV & FTC/3TC Resistance
  - 65R + 184V on same genome
  - TNV 2-3 fold; 3TC/FTC > 100-fold

What will be the outcome if TNV/FTC-containing ART & ARP Are Rolled Out?



This?

Train Wreck

- Rapid rise in prevalence of transmitted and acquired resistance to TNV and FTC/3TC (XTC)
  - 65R, 184V, both
- Reduced efficacy of first-line ART & TNV/XTC-based ARP
- Less public benefit from ART and ARP
  - Rising mortality from AIDS
  - Multidimensional fallout
    - » Pyschological, political, fiscal….

Or better this?

Key Unanswered Questions

- Transmissibility of HIV with 65R, 184V or both?
  - Probably reduced compared with wildtype
- Activity of TNV or TNV/XTC vs. 65R, 184V or both?
  - XTC not likely to be very effective vs. 184V
  - TNV not likely to be very effective vs. 65R
    - » But high concentrations in TNV gel may be effective
  - TNV likely effective vs. 184V (more than vs. widltype)
- Kinetics of emergence of 65R & 184V in persons infected while on ARP with TNV or TNV/FTC

Key Unanswered Questions

- Persistence of 65R & 184V after d/c of TNV/FTC
  - Mutants are less fit than wildtype and likely to decline rapidly in frequency, but to what level?
- Mutant frequency within an individual that affects treatment response to TNV/XTC-containing ART
  - Similar or different from NVP?

Recent Insights from sdNVP for MTCT

A5208/OCTANE Study Design

Trial 1: 240 women prior SD NVP ≥ 6 months

- LPV/r + TDF/FTC n=120
- NVP + TDF/FTC n=120

Trial 2: 500 women with NO prior SD NVP

- LPV/r + TDF/FTC n=250
- NVP + TDF/FTC n=250

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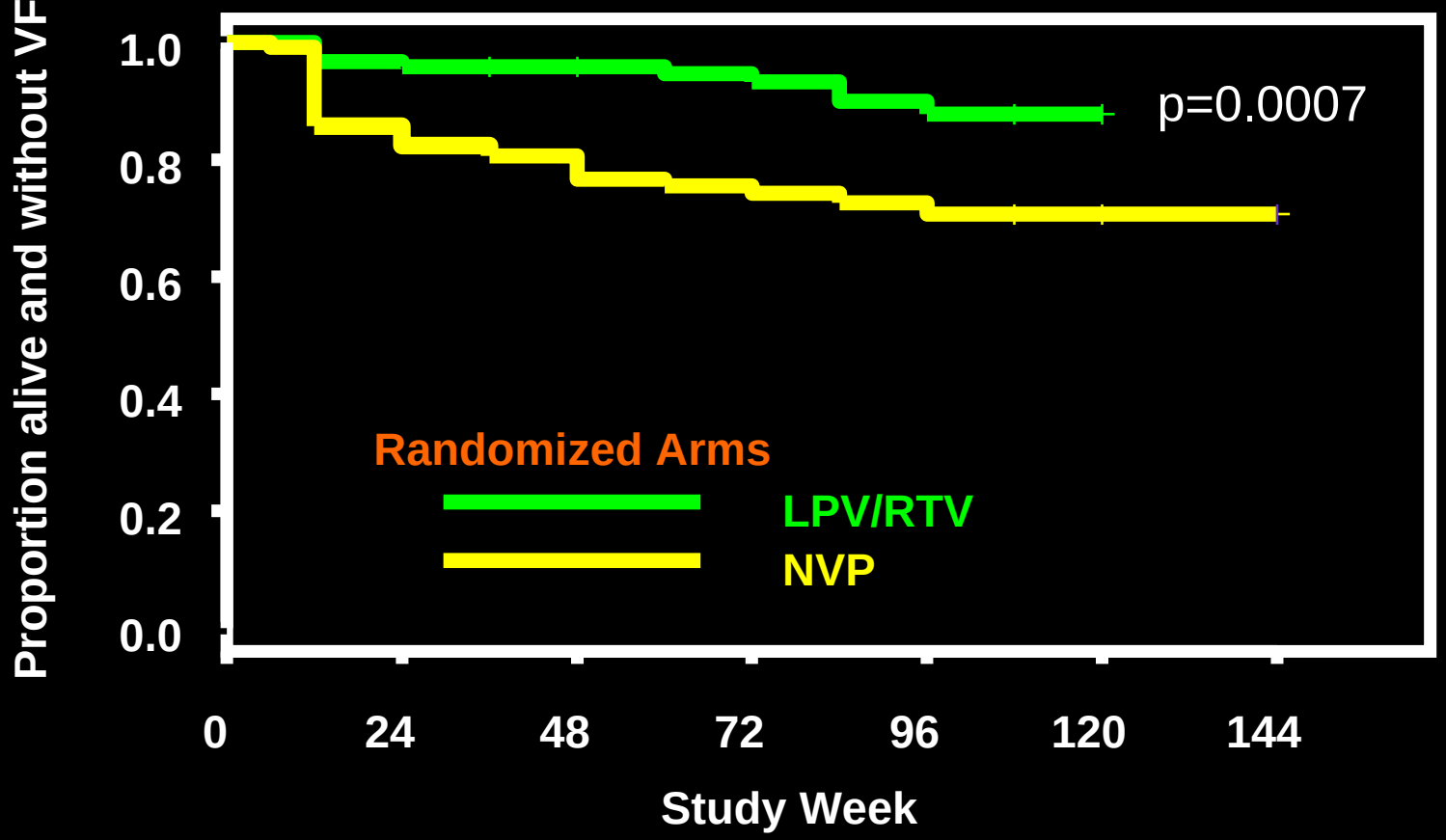
KM Plot of Time to Primary Endpoint (Virologic Failure or Death)

- 41 women reached an endpoint:
  - 31 (26%) in NVP and 10 (8%) in LPV/r arms
- Hazard ratio 3.55 **(95% CI 1.71, 7.34)**



Lockman et al.

CROI 2009

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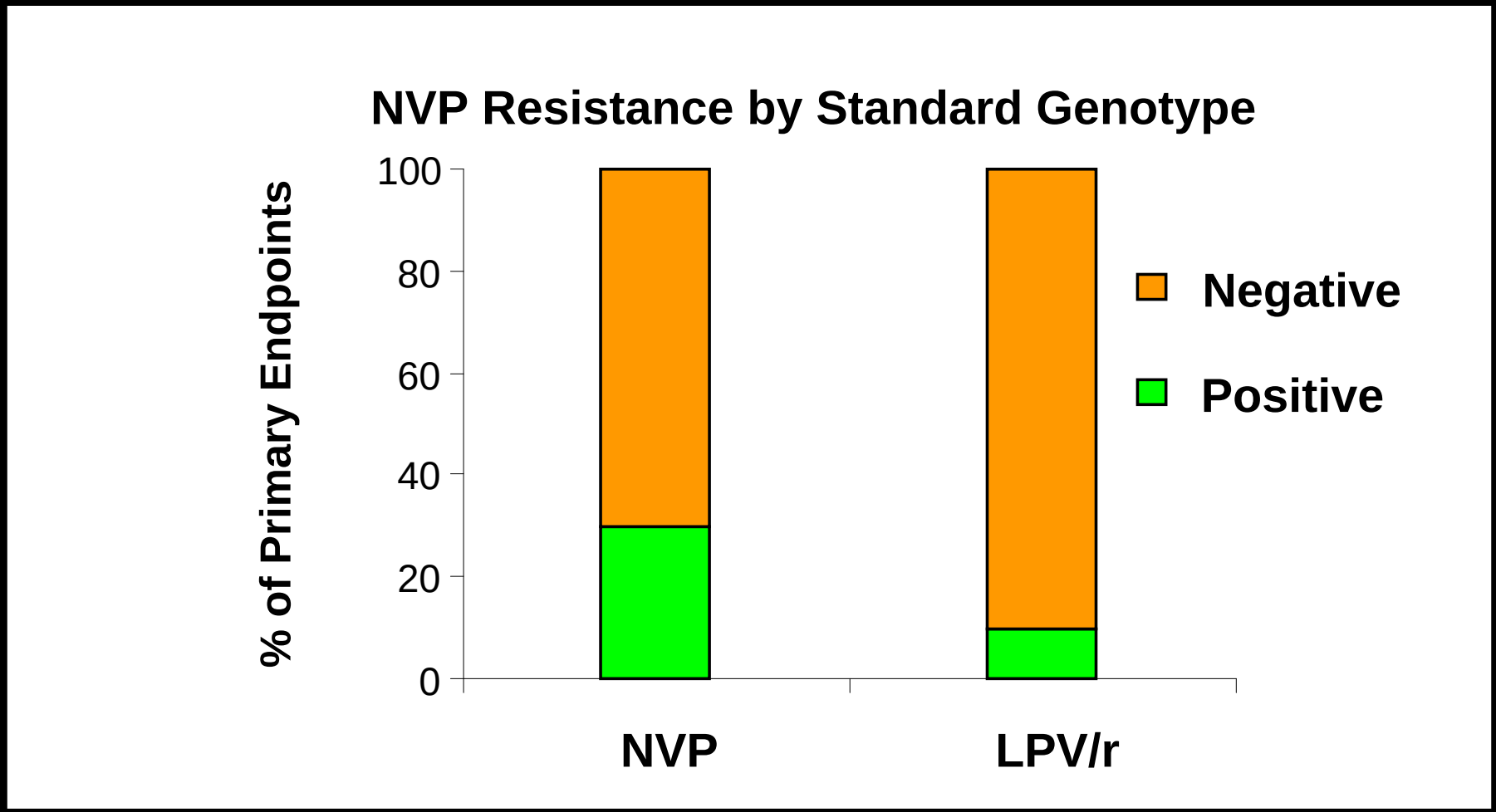
Most Endpoints Occurred in Women without Baseline NVP Resistance by Std Genotype



Hypothesis

The excess failure in the NVP arm is due, in part, to low frequency NVP-resistant variants that are missed by standard genotyping.

⇒Use allele-specific PCR (ASP) to detect NVP-resistant variants with greater sensitivity

0.1% at RT codons 103 and 190 and

0.3% at RT codon 181

Palmer et al. AIDS 2006; 20: 701-710

ASP Predicts a Primary Endpoint of NVP- containing ART Following Exposure to sdNVP (All Patients)

Arm	NVP resistance	Number of subjects	Number of Primary Endpoints	P Value Subgroup Analysis	Hazard Ratio (95% CI)
NVP (N=114)	ASP +	51	21 (41%)	0.004	3.30 (1.48,7.39)
	ASP -	63	9 (14%)		
LPV/RTV (N=118)	ASP +	49	4 (8%)	0.99	0.99 (0.28,3.56)
	ASP -	69	6 (9%)		

Conclusions and Implications

- The risk of failure after sdNVP for NVP-containing ART cannot be fully predicted by clinical history (time since exposure) or standard genotype
- Excess failure in the NVP arm is largely explained by NVP-resistant mutants not detected by standard resistance testing
- NVP-resistant mutation frequencies >0.8% are significantly associated with increased risk of a primary endpoint.
- The frequency of NVP resistance declines with time after sdNVP, but the risk of failure for a specific frequency of mutant does not

Thoughts on Minimizing Casualties

- Much is at stake!
- Expect resistance and be prepared for it
  - Monitor, detect with sensitive methods, track outcomes
- Don’t play a blame game re: where it came from
  - Partner with ART advocates
- PREVENT ARP USE IN HIV POSITIVES
  - Link ARP to VCT
  - Educate re: dangers of sharing product
- Develop alternatives to TNV/FTC ASAP!
  - Topical combination products (NRTI + Entry I, NNRTI, Int I)
  - Oral and parenteral products (Entry I, Int I, NNRTI)

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