Kirby Institute

Relationship between untimed plasma lopinavir concentrations and virological outcome on second-line antiretroviral therapy

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Background

UNSW SYDNEY Kirby Institute

Optimal adherence is critical for virological suppression for both 1st and 2nd line ART regimen.

In LMICs, poor adherence has been associated with high rates of virological failure to 2nd line regimen.

Ajose, Olawale, et al. AIDS (2012)

Updated 2016 WHO guidelines

Recommendations for Public Health Approach

4.8 What ART regimen to switch to (second- and third-line ART)

Table 4.15. Preferred second-line ART regimens for adults, adolescents, pregnant women and children

Population		Failing first-line regimen	Preferred second-line regimen	Alternative second-line regimens
Adults and adolescents		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r[c]
		2 NRTIs + DTG		
Pregnant or breastfeeding women		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + ATV/r or LPV/r	2 NRTIs[b] + DRV/r
Children	Less than 3 years	2 NRTIs + LPV/r	2 NRTIs[b] + RAL	Maintain the failing LPV/r-based regimen and switch to 2 NRTIs[b] + EFV at 3 years of age
		2 NRTIs + NVP	2 NRTIs[b] + LPV/r	2 NRTIs[b] + RAL[d]
	3 years to less than 10 years	2 NRTIs + LPV/r[a]	2 NRTIs[b] + EFV	2 NRTIs[b] + RAL[d]
		2 NRTIs + EFV (or NVP)	2 NRTIs[b] + LPV/r	2 NRTIs[b] + ATV/r[d]

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- Prohibitive cost of viral load testing and resistance testing
- Identifying the non-adherence is crucial for reaching the 3rd "90" target.

Challenge in measuring adherence

- Adherence changes over time
- Some ART are forgiving(including boosted PIs)
- Shuter, J. *Antimicrobial Chemotherapy* (2008)
- Adherence threshold for maintaining durable suppression
- Self reported – bias and over-estimation

Background

Untimed plasma concentration of PIs

- Predict resistance in LPV/R based ART

Court, Richard, et al (2016)

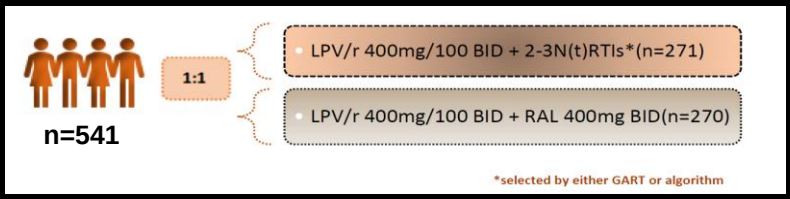
- Undetectable plasma concentration predict virological failure in low level viraemia

Gonzalez-Serna, A., et al (2016)

Background

The SECOND-LINE main study**

- Adults ≥16 years old
- Confirmed virological failure of NNRTI+2N(t)RTIs (pVL >500 copies/mL)
- No prior PI or InSTI exposure
- Stratified by site and baseline pVL >100,000 c/mL



***Second-Line Study Group. "Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-LINE): a randomised, open-label, non-inferiority study." The Lancet (2013).*

***Amin, Janaki, et al. "Raltegravir non-inferior to nucleoside based regimens in second-line therapy with lopinavir/ritonavir over 96 weeks: a randomised open label study for the treatment of HIV-1 infection." PloS one(2015).*

Background

The SECOND-LINE resistance study**

- Virological failure in the SECOND-LINE trial was associated with:
- Self-reported non-adherence
- Higher baseline gGSS
- Higher baseline VL >100,000 copies/mL
- Ethnicity

**Boyd, Mark A., et al. "Baseline HIV-1 resistance, virological outcomes, and emergent resistance in the SECOND-LINE trial: an exploratory analysis." The Lancet HIV (2015)

Hypothesis

- Untimed plasma lopinavir concentration (UPLC) measured at week 12 would predict virological failure at 48 weeks in the SECOND-LINE Study
- Does ethnicity really matter?

Primary Objective

To investigate the association between untimed detectable lopinavir concentration (LPV≥25 µg/L) or undetectable (LPV<25 µg/L) LPV plasma levels at week 12 and virological failure at week 48 (VL ≥ 200 copies/mL).

Secondary Objectives

- To investigate the association between UPLC at week 12 and time to loss of virological response [TLOVR] over 48 weeks.

Methods

- "Untimed" WK 12 plasma LPV concentration using stored patient samples from the SECOND-LINE study .
- HPLC - LLD of 25 µg/L
- UPLC categorized as (using LLD and DHHS guidelines)

i. Detectable (≥25 µg/L)

ii. Undetectable (u-UPLC) (<25 µg/L)

- Detectable was further categorized as

(a) detectable and optimal (o-UPLC) (≥1000 µg/L)

(b) detectable but sub-optimal (s-UPLC) (≥25 to <1000 µg/L)

Methods

- A chi-square - association between UPLC and virological outcome at week 48
- Regression - association between VF at week 48, UPLC and other predictors of virologic outcome** (age, BMI, sex, ethnicity, duration of HIV infection, HIV stage, duration of ART, randomized arm, baseline VL, nadir CD4, baseline CD4, baseline CD8, baseline CD4/CD8 ratio, adherence at week 4, adherence at week 48, baseline resistance (genotypic sensitivity score [GSS]) and HIV subtype).
- Cox regression - relationship between UPLC and TLOVR

Results

Baseline characteristics:

- **N=517**
- **Median age38(32,44)years,**
- **54% males,**
- **50% RAL+LPV/r, 50% N(t)RTIs+LPV/r**
- **At week 12, 32/517 (6%) had undetectable UPLC, and 485/517 (94%) had detectable UPLC**
- **Ethnicity (Asian 46.9%, Hispanic 15.6%, African 28.1% Caucasiann9.4%)**

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Results

Significant association between UPLC and virological outcome

UPLC (µg/L)	Virological failure N (%)	Viral suppression N (%)	Total N (%)
Undetectable	15(22.1)	17((3.8)	32(6.19)
Detectable	53(77.9)	432(96.2)	485(93.8)
Total	68(100)	449(100)	517(100)
X^2 (1) = 18.51 p <0.001			

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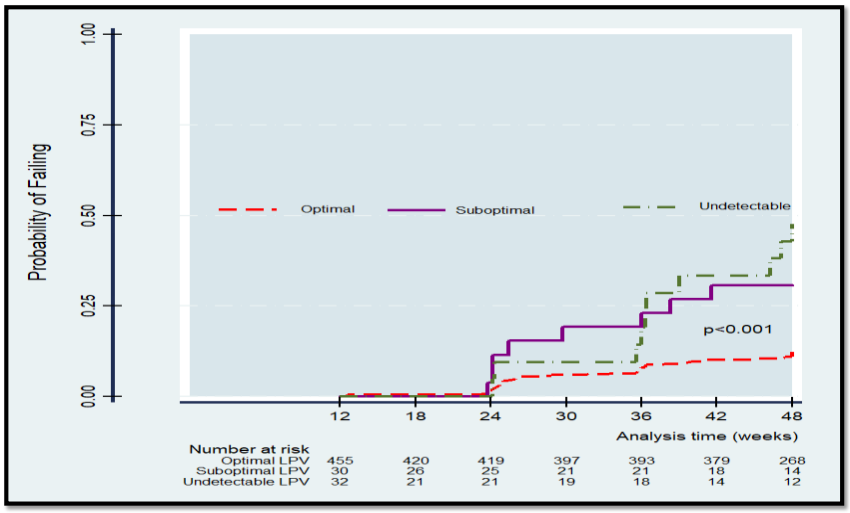
Results

Undetectable UPLC was associated with higher rate of virological failure over 48 weeks.



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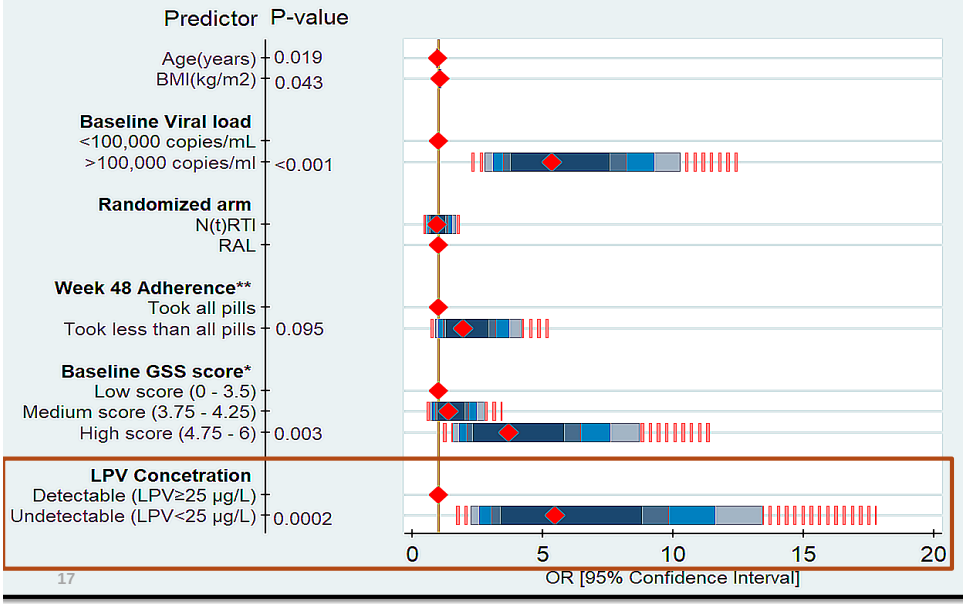
Undetectable UPLC independently predicted virological failure at week 48



Conclusion

Untimed plasma concentration in LMCIs

- Early and objective identification of non adherence
- Ethnicity on it's own is not predictive
- Optimize 2nd line treatment outcome through adherence stewardship
- Sustainability of ART treatment programs
- 90 – 90 -90 targets

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- Thank you