Re-evaluation of resistance algorithms for lopinavir/ritonavir in the TITAN trial

Andrew Hill,[1] Anne-Geneviève Marcelin,[2] Vincent Calvez[2]

[1]University of Liverpool, Liverpool, UK; [2]Université Pierre-et-Marie-Curie, Paris, France

Address correspondence to: Andrew Hill, University of Liverpool, Liverpool, UK; E-mail: microhaart@aol.com

Abstract

Background: Genotypic algorithms used to predict the clinical efficacy of lopinavir/ritonavir (LPV/r) have included a range of mutation lists and efficacy endpoints. HIV clinical trials are normally powered to detect a difference between treatment arms of 10–12% for the endpoint of HIV-1 RNA suppression <50 copies/mL. The TITAN trial (TMC114-C214) evaluated LPV/r versus darunavir/ritonavir (DRV/r) in treatment-experienced patients with HIV-1 RNA >1,000 copies/mL.

Methods: Baseline genotype data were classified using five genotypic resistance algorithms: IAS-USA LPV mutations (cut-off=6), Abbott 2007 mutation list (cut-off=3), ANRS mutations (cut-off=6), FDA mutations (cut-off=3) and IAS-USA major protease inhibitor (PI) mutations. Efficacy in the TITAN trial (HIV-1 RNA <50 copies/mL at Week 48) was correlated with the number of mutations from each list, to show the 'efficacy advantage cut-off level': the number of mutations from each list associated with a difference in efficacy between treatment arms of at least 12%. The linearity of the correlation between mutation count and efficacy of LPV/r was analysed in TITAN, with sensitivity analysis for the French LPV ATU, BMS-045 and RESIST trials.

Results: In TITAN, the concordance between baseline LPV resistance, defined by the mutation scores, ranged from 79–95%. Multivariate analysis identified lower than previously reported genotypic cut-off levels where there was at least 12% lower efficacy for LPV/r versus DRV/r. These 'efficacy advantage cut-off levels' were: IAS-USA LPV mutations (cut-off=3); Abbott 2007 (cut-off=2); ANRS LPV mutations (cut-off=3); FDA LPV mutations (cut-off=2), and major IAS-USA PI mutations (cut-off=1). There were linear falls in HIV-1 RNA suppression rates with rising mutation counts in the TITAN, French LPV ATU, BMS-045 and RESIST trials.

Conclusions: The analysis identified more sensitive 'efficacy advantage cut-off levels' for four LPV genotypic algorithms, below those currently used, at which there is significant efficacy advantage for treatment with DRV/r versus LPV/r in the TITAN trial.

Background

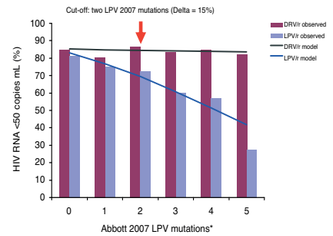
- Genotypic algorithms for LPV have been established with different cut-off levels for response, and often with log reduction or suppression <400 copies/mL of HIV RNA as the efficacy endpoint.
- This analysis aims to re-evaluate these algorithms using a standardised HIV RNA <50 copies/mL endpoint at 48 weeks (consistent with regulatory guidelines on efficacy).
- The analysis aims to identify 'efficacy advantage cut-off levels' where DRV/r shows greater efficacy than LPV/r. Clinical trials are powered to show at least a 10–12% difference in efficacy between treatment arms, so this was used as the threshold delta to define the cut-off levels.
- Also, the linearity of correlation between rising mutation numbers and efficacy was assessed in the TITAN,[1] BMS-045,[2] French LPV ATU[3] and RESIST[4] trials.

Methods

- TITAN was an open-label, Phase 3, randomised, non-inferiority trial comparing DRV/r 600/100mg bid vs LPV/r 400/100mg bid in 595 treatment-experienced, LPV-naïve patients with baseline HIV RNA levels above 1,000 copies/mL.[1] Patients also received optimised reverse transcriptase inhibitors, selected on the basis of treatment history and screening resistance tests.
- The TITAN patients were 79% male and 55% Caucasian with a mean age of 41 years. The median baseline CD4 cell count and HIV RNA level were 232 cells/µL and 4.31 $\log_{10}$ copies/mL, respectively. Sixty-nine per cent of the patients had previously used at least one PI, and 10% had at least 10-fold phenotypic resistance to LPV at baseline. Baseline levels of genotypic and phenotypic resistance to DRV, LPV and NRTIs were well balanced between the arms.
- After 48 weeks, the percentage of patients with HIV RNA <50 copies/mL in the overall intent-to-treat (ITT) analysis was 71% in the DRV/r arm vs 60% in the LPV/r arm ($p<0.01$).[1] HIV RNA suppression rates did not correlate with the number of phenotypically sensitive reverse transcriptase inhibitors in the background regimen.
- The efficacy in the DRV/r and LPV/r arms was summarised by baseline genotypic and phenotypic resistance, by the following algorithms
  - IAS-USA LPV mutation list[5]
  - Abbott 2007 LPV mutation list[3]
  - ANRS mutations[6]
  - FDA LPV mutation list[7]
  - IAS-USA primary PI mutation list[5]
  - Stanford LPV algorithm[8]
  - REGA LPV mutation list[9]
- There is substantial overlap between these lists. For example, of the 17 mutations in the current IAS-USA list associated with resistance to LPV, 10 are also IAS-USA primary PI mutations.[5]
- An ITT time-to-loss of virological response (TLOVR) analysis was used, with an endpoint of HIV RNA suppression <50 copies/mL. Multivariate correlation was used, controlling for baseline CD4 cell count, HIV RNA and prior PI use.

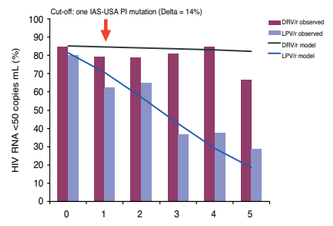
Results

TITAN – HIV RNA <50 copies/mL at Week 48 by number of Abbott LPV 2007 mutations[3] (ITT non-VF censored analysis)



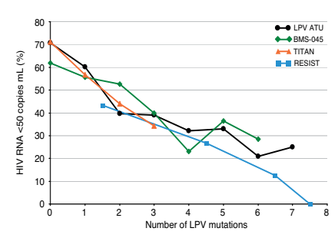
*L10, K20, L24, L33, M36, I47, G48, I54, V82 and I84[3]

TITAN – HIV RNA <50 copies/mL at Week 48 by number of major IAS-USA PI mutations[5] (ITT non-VF censored analysis)



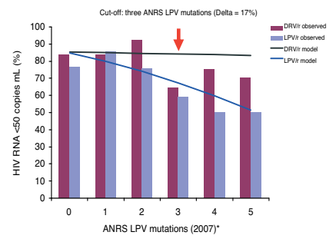
*D30N, V32I, L33F, M46I/L, I47V, G48V, I50V/L, I54V/L/M, L76V, V82A/F/S/T, I84V, N88S and L90M[5]

TITAN, BMS-045, French LPV ATU and RESIST trials – HIV RNA response to LPV/r at Week 48 by number of LPV mutations: evidence for linear correlation between mutations and response



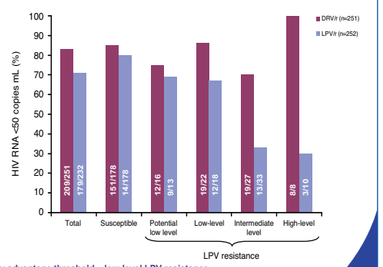
TITAN = IAS-USA LPV mutations list[5]; BMS-045 = FDA LPV mutations list[7]; French LPV ATU = French LPV ATU list[3]; RESIST = Abbott 2001 list[10]

TITAN – HIV RNA <50 copies/mL at Week 48 by number of ANRS LPV mutations[6] (ITT non-VF censored analysis)



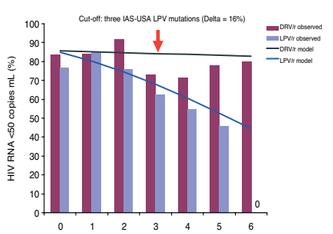
*L10F/I/V/R, K20M/R, L24I, L33F, M46I/L, I47A, I50V, F53L, I54V/L/M/T/S, L63P, A71L/V/T/I, L76V, V82A/F/S/T, I84V and L90M[6]

TITAN – HIV RNA <50 copies/mL at Week 48 by Stanford LPV algorithm[8] (ITT non-VF censored population)



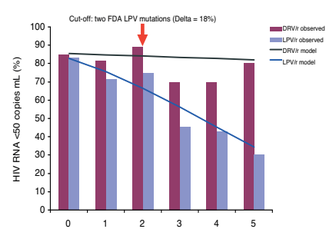
Efficacy advantage threshold – low-level LPV resistance

TITAN – HIV RNA <50 copies/mL at Week 48 by number of IAS-USA LPV mutations[5] (ITT non-VF censored analysis)



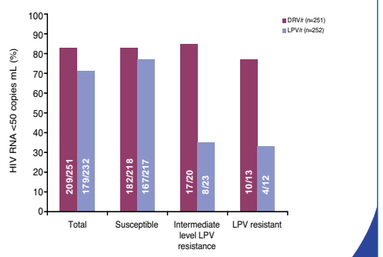
*L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54V/L/M/S/T, L63P, A71V/T, G73V, L76V, V82A/F/S/T, I84V and L90M;[5] VF = virological failure

TITAN – HIV RNA <50 copies/mL at Week 48 by number of FDA LPV mutations[7] (ITT non-VF censored analysis)



*L10F/I/R/V, K20M/N/R, L24I, L33F, M36I, I47V, G48V, I54V/L/T, V82A/C/F/S/T and I84V[7]

TITAN – HIV RNA <50 copies/mL at Week 48 by REGA LPV algorithm[9] (ITT non-VF censored population)



Efficacy advantage threshold – intermediate LPV resistance

- This analysis identifies new cut-off levels where DRV/r shows higher rates of full HIV RNA suppression (at least 12% superior to LPV/r), based on the TITAN results.

Algorithm	Current cut-off	Efficacy advantage cut-off
IAS-USA LPV mutations[5]	6	3
Abbott 2007 LPV mutations[3]	3	2
ANRS mutations[6]	6	3
FDA LPV mutations[7]	3	2
IAS-USA primary PI[5]	N/A	1
Stanford LPV algorithm[8]	N/A	Low-level LPV resistance
REGA LPV mutations[9]	N/A	Intermediate LPV resistance

N/A = not applicable

Conclusions

- Previous cut-off levels for defining susceptibility to antiretrovirals have often been based on analysis of continuous log reductions in viral load and early timepoints.[11] New breakpoints for interpretation of genotypic information should now be based on full HIV RNA suppression <50 copies/mL.
- There was a linear fall in efficacy of LPV/r with rising numbers of mutations, starting even with a single mutation, in the TITAN, French LPV ATU, BMS-045 and RESIST trials.
- This analysis shows that diminished LPV efficacy manifests with fewer LPV mutations than has previously been demonstrated.

References

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