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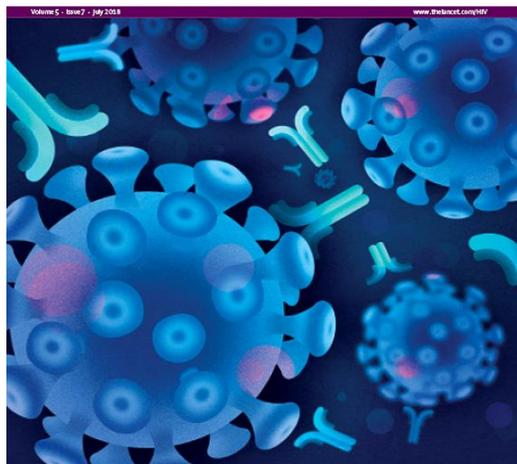
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Please contact may.wang@ashm.org.au for details.

The Lancet HIV

Dr Niveditha Manokaran: CMO, RPA Sexual
Health Centre

THE LANCET
HIV



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Wild-type infection despite PrEP: a lot to learn from a case report

Darcis G et al, 5(1), Jan 2018

Background

- Response to a case study of acquisition of wild-type HIV-1 infection in a patient on PrEP
- The patient acquired wild type infection despite high levels of tenofovir diphosphate
- Uncertainty of actual infection with initial gp160 detected on western blot
- Diagnosis of acute HIV infection was questioned
- Coincided with diagnosis of rectal LGV – several preceding episodes of proctitis
- Partners had increased since starting PrEP 8 months before
- Several presentations with proctitis

What are the favourable outcomes?

- Low/absent immune activation
- Low/absent viral reservoir size and diversity also could impede acquisition of mutations thereby conserving a better chance to response to potential cure strategies

What was missed?

- PrEP was ceased and further testing were performed to confirm the diagnosis, however the opportunity to start ARV at seroconversion was missed

Relevance

- Despite demonstrated efficacy of PrEP, the wide spread uptake could mean this unprecedented event may happen again
- Reflect on possible profile of patients with risk compensation behaviour – different/ closer follow up may be required

Which HIV-infected adults with high CD4 T-cell counts benefit most from immediate initiation of antiretroviral therapy? A post-hoc subgroup analysis of the START trial

Molina JM et al, 5(4), April 2018

Background/aim

- Immediate initiation of ART not always be possible in resource-limited settings
- Study aimed to identify subgroups of individuals who would benefit most from immediate treatment

Methods

- RCT of asymptomatic HIV +ve adults untreated with ART (**START**) > immediate and deferred ART
- Primary endpoint – serious AIDS defining illness or non-AIDs related death
- Post hoc analysis of estimating event rates and absolute risk reduction with immediate vs deferred ART
- Heterogeneity in absolute risk reduction (ARR) between subgroups assessed with bootstrap tests

Results

- Overall 4684 participants, Immediate ART: 2325 and deferred ART: 2359
- 42 primary events occurred in immediate ART group over 3.1 yrs compared with 100 events in deferred ART group
- ARR was 0.8% per 100 person years (95% CI 0.48-1.13) with immediate treatment
- 126 people would need treatment immediately to prevent one event (95% CI 89-208)
- Significant heterogeneity in ARR with immediate ART found across subgroups according to age ($p=0.0022$), CD4 to CD8 ratio ($p=0.0007$) and plasma HIV RNA VL at baseline ($p=0.033$)

Conclusion

- Consistent with the finding of the main study
- Identified subgroups of participants who have the greatest reduction in AR from Immediate ART
- Asymptomatic ART-naïve adults with CD4 counts higher than 500 who are older, have a low CD4 to CD8 ratio, or High plasma VL benefit most from immediate initiation of ART and should be prioritised for treatment

Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial

Winston A et al, 5(4), April 2018

Background

- Study aimed to compare safety and efficacy of TAF plus emtricitabine with that of abacavir plus lamivudine

Method

- Randomised, double-blind, active-controlled, non-inferiority phase 3 trial among HIV-1-positive adults (≥18 years)
- Eligibility > virologically suppressed (VL <50 copies) and on a stable three-drug regimen containing abacavir plus lamivudine
- Participants randomly assigned to switch to fixed-dose tablets
- The primary endpoint - proportion of participants with virological suppression at week 48

Tenofovir alafenamide plus emtricitabine versus abacavir plus lamivudine for treatment of virologically suppressed HIV-1-infected adults: a randomised, double-blind, active-controlled, non-inferiority phase 3 trial

Cont

Results

- 501 participants were randomly assigned and treated during study period June 2015-May 2016
- Virological suppression maintained in 90% of 253 participants receiving TAF + FTC compared with 93% of 248 receiving abacavir + lamivudine (difference -3.0%, 95% CI -8.2 to 2.0)
- 4% of 280 in the TAF + FTC group and 3% of 276 in the abacavir plus lamivudine group stopped treatment due to adverse events
- Changes in Hip and Lumbar spine BMD were minimal
- Minimal and similar changes in creat. Clearance, retinol-binding Prot: Creat ratio, B2 microglobulin to creat ratio
- Treatment emergent proteinuria less in TAF (2%) vs abacavir+lamivudine group (7%)
- No difference in total cholesterol, LDL, HDL and TGL in TAF

Conclusion

- TAF+FTC and some third drugs maintained high efficacy with renal and bone safety similar to abacavir
- In virologically suppressed patients a regime containing TAF is an alternative to regimes containing abacavir without concern for new onset renal or bone toxicities or hyperlipidaemia

Efficacy and safety of varenicline for smoking cessation in people living with HIV in France (ANRS 144 Inter-ACTIV): a randomised controlled phase 3 clinical trial
Mercié P et al, 5(3), Mar 2018

Background

- Tobacco smoking is common in people living with HIV
- Lack of high quality evidence of interventions for smoking cessation
- Assess the efficacy and safety of varenicline (campix) with counselling to aid smoking cessation among people living with HIV

Methods

- Randomised, parallel, double-blinded, placebo controlled trial (France)
- HIV, smoked 10 or more cigarettes daily for >1 year – motivated to stop
- Allocated to receive 0.5mg doses x2 or placebo BD + counselling (12 weeks)
- Primary outcome >% of participants abstinent from week 9 to week 48
- Intention to treat (ITT) and modified ITT (mITT) analysis model

Efficacy and safety of varenicline for smoking cessation in people living with HIV in France (ANRS 144 Inter-ACTIV): a randomised controlled phase 3 clinical trial
cont

Findings

- 248 patients > 123 assigned to treatment and 125 assigned to placebo
- ITT analysis campix associated with higher % achieving abstinence over study period
- 18 (15%) patients (95% CI 8-21) in treatment group vs 8(6%) (95% CI 2-11) in placebo group - AOR 2.5 (95% CI 1.0-6.1, p=0.041)
- Depression incidence 2.4 per 100py (95% CI 0.6-9.5) in campix group vs 12.4 100py (95% CI 6.9-22.5)
- GI and psychiatric effects : AEs mainly grade 1/2, 7% had grade 3/4
- No effect on HIV status (Well controlled VL and CD4 range through out the study)

Conclusion

- Campix is safe and efficacious for smoking cessation in PLWHIV
- In association with individualised counselling is a convenient and effective option that is safe and has no clinical interaction with ARV drugs

Predictors of linkage to HIV care and viral suppression after release from jails and prisons: a retrospective cohort study

Loeliger KB et al, 5(2) Feb 2018

Background

- Incarceration > improved engagement in HIV care but poor ART outcomes on release
- US study aimed to assess factors relating to linkage to care (LTC) post release

Methods

- Retrospective cohort of HIV adults released from prisons between 2007-2014, Connecticut, USA
- Data linkage > administrative custody and pharmacy data systems with HIV/AIDS surveillance and case management data
- Study examined time to LTC and viral suppression at LTC
- GEE analysis to show predictors of LTC within 14 and 30 days of release

Predictors of linkage to HIV care and viral suppression after release from jails and prisons: a retrospective cohort study

cont

Findings

- 3302 incarceration periods for 1350 individuals between 2007 and 2014
- 21% had LTC within 14 days of release and 34% had LTC within 30 days of release
- 29% had detectable viral loads at LTC
- Factors positively associated with LTC within 14 days of release:
 - Intermediate (31–364 days) incarceration duration (AOR 1.52, CI 1.19-1.95)
 - Transitional case management , receipt of antiretroviral therapy during incarceration (AOR 1.65, CI 1.36-1.991-39)
 - Two or more medical comorbidities (1.86, CI 1.48-2.36))
- Re-incarceration and conditional release negatively associated with LTC within 14 days

Conclusion

- LTC is suboptimal
- Consistent targeted provision of transitional case management and integration of health-care and criminal justice services are key to the improvement of HIV treatment outcomes during and after the transition to community settings

South Australian prison officer Sashi Cheliah



**The effect of antiretroviral intensification with
dolutegravir on residual virus replication in HIV-
infected individuals: a randomised, placebo-controlled,
double-blind trial**

Rasmussen TA et al, 5(4), April 2018

Background and study aim

- Unclear if virus replication occurs in HIV patients on ART
- Unknown if residual virus replication is a barrier to achieving a cure for HIV
- RCTs x2 - raltegravir had been investigated in ART intensification trials reported increase in 2-long terminal repeat (2-LTR) circles
- Dolutegravir, second generation, once-daily INSTI that is safe and highly potent
- RCTs - dolutegravir non-inferior to raltegravir for the outcome of virological suppression in treatment naïve patients
- Superior to raltegravir in a treatment experienced population not exposed INSTI

Study aim

- To establish whether ART intensification with dolutegravir would inhibit residual virus replication in HIV-infected individuals on ART
- Study compared the effect of intensification with dolutegravir or placebo in HIV-infected individuals on suppressive ART

What are 2-LTR circles?

- **2-LTR circles** are referred to repeatedly throughout the study
- LTR stands for **long terminal repeats**
- Identical sequences of DNA that repeat hundreds or thousands of times found at either end of retrotransposons or proviral DNA formed by reverse transcription of retroviral RNA
- Used by viruses to insert their genetic material into the host genomes
- Integrase inhibitors block the integration of linear HIV DNA, which subsequently becomes circularised by host repair enzymes to form **2-LTR circles**
- An increase in **2-LTR circles** occurs when active replication is inhibited through blocking integration
- **2-LTR circles** have a short half-life
- Could explain why an **increase in 2-LTR circles** only recorded in studies that measured **2-LTR circles within 2 weeks** (raltegravir intensification)

Methods

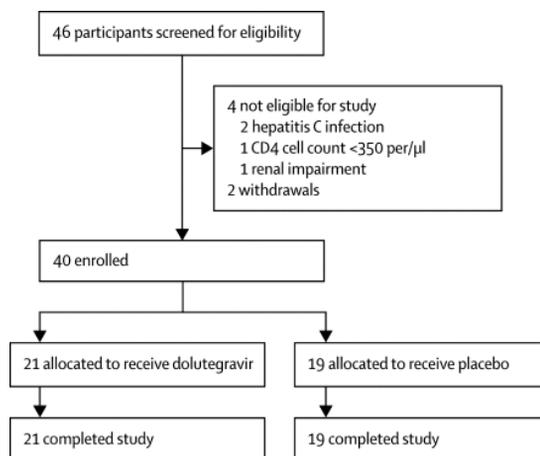
Study design and participants

- Investigator-initiated, randomised, placebo-controlled, double-blinded trial
- Participants > HIV-infected adults receiving ART for at least 3 years with no change in regime in last 6 months (Melbourne)
- CD4 counts >350 cells per μL and
- Virological suppression for at least 3 years
- Exclusion criteria
 - hepatitis C co-infection, unstable liver disease, renal impairment
 - GI disorders that would affect the absorption of study treatment
 - Current or previous use of any integrase inhibitor
 - Current or previous use of any latency-reversing agent
 - Current use of drugs with significant interactions with dolutegravir
 - Pregnant or breastfeeding women

Methods

Randomisation and masking

- Participants randomly assigned to receive dolutegravir or placebo (1:1)
- Stratified by current use of PI



Methods

Procedure

- Participants received 50mg dolutegravir or matching placebo daily for 56 days (continued current ART)
- Follow up serology on day 1, 3, 7, 14, 28, 56, and 84 after commencing study drug
- Adherence checked each visit and plasma concentrations checked day 7 (treatment arm)
- Adverse events recorded
- Clinical review and further monitoring days 14, 28, 56, and 84 (e.g. LFTs, vital signs)
- Isolated CD4 cells were lysed and lysates stored at -80°C until analysed
- 2-LTR circles analysed from DNA extracted from cell lysates
- Primary analysis, the mean of three (HIV DNA assays) and four (cell-associated unspliced HIV RNA) replicates measured as CCR5 copy number and 18S expression
- Negative binomial regression analysis individual replicates > outcome variable, input cell number > exposure variable

Methods

Procedure cont

- Flow cytometry and fluorescence activated cell sorting used to quantify markers of T-cell activation and exhaustion
- High-sensitivity C-reactive protein (hsCRP) analysed by a standard clinical assay
- Dolutegravir in plasma measured by Pharmaceutical Product Development (LLC, Middleton, WI, USA)
- Analytes were isolated through protein precipitation
- A linear, 1/concentration weighted, least-squares regression algorithm was used to quantitate unknown samples

Outcomes

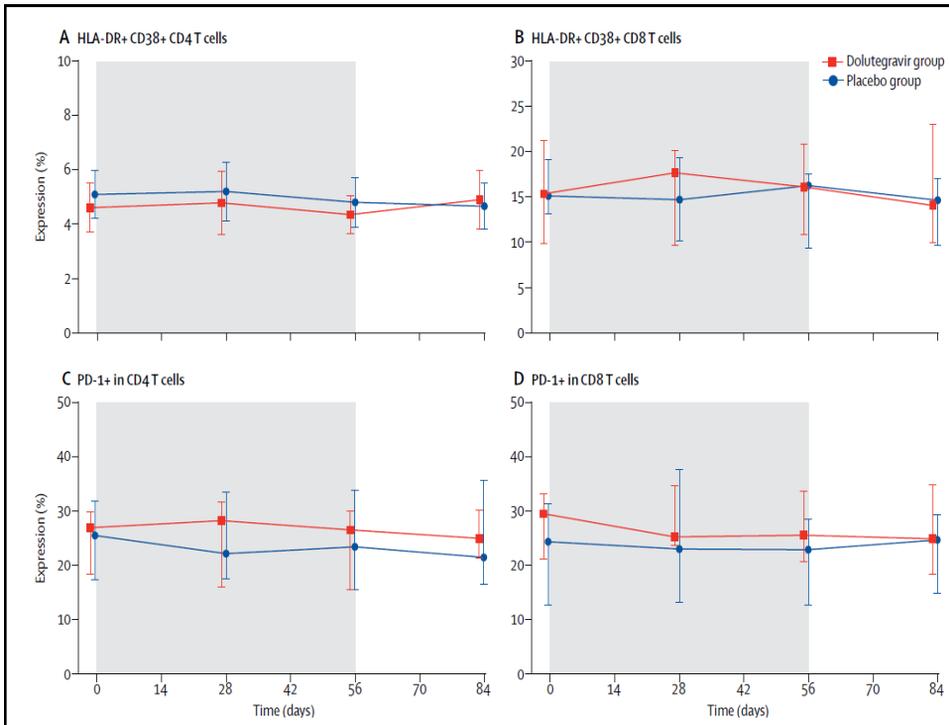
- Primary outcome > measure change from baseline of the frequency of 2-LTR in peripheral blood CD4 cells after 7 days of ART intensification with dolutegravir vs placebo
- Secondary virological outcome > change from baseline in the frequency of 2-LTR in CD4 cells at other timepoints during follow-up, low-level HIV viraemia
- Secondary immunological outcome > change from baseline in T-cell activation and exhaustion as measured by expression of HLA-DR, CD38, and PD-1 in populations of CD4 cells and CD8 cells with flow cytometry
- Safety > secondary outcome measure assessed by the incidence and severity of adverse events

Results - baseline characteristics

Sept 2015-2016	Dolutegravir group (n=21)	Placebo group (n=19)
Age (years)	49.4 (10.8)	48.5 (8.0)
Sex		
Men	18 (86%)	19 (100%)
Women	3 (15%)	0
Baseline CD4 count (cells per μ L)	721 (648–953)	664 (545–891)
Regimen		
Non-nucleoside reverse transcriptase inhibitor	18 (86%)	17 (89%)
Protease inhibitor	3 (14%)	2 (11%)

Results

- No significant difference between dolutegravir and placebo in change from baseline of 2-LTR circles in peripheral blood CD4 cells
- Statistical methods did not identify a significant increase in 2-LTR circles in the dolutegravir group relative to placebo at any of the timepoints from baseline to day 84
- No change from baseline to day 7 in either group in the proportion of samples with undetectable levels of 2-LTR
- Additional virological analyses of cell-associated unspliced HIV RNA, total HIV DNA, integrated HIV DNA, and plasma HIV RNA (as measured by the single copy assay) by repeated measures ANOVA showed no significant difference in the change from baseline to any timepoint between the dolutegravir and placebo group - see figure



Results

- Minor increase in PD-1 expression in CD4 cells from baseline to day 56 in the dolutegravir group compared with placebo ($p=0.03$)
- No difference in PD-1 expression in CD8 cells in the change from baseline to any timepoint during study therapy
- No significant differences in the change from baseline between study groups in other T-cell markers of immune activation
- No difference between study groups in the change from baseline to any timepoint in plasma levels of sCD14, d-dimer, IL-6 or hsCRP
- Addition of dolutegravir to pre-existing ART regimens was safe
- No patients discontinued treatment or reported treatment-related serious adverse events
- All clinical and laboratory treatment-related adverse events were mild (grade 1)
- Dolutegravir trough concentrations at day 7 confirmed adherence to study treatment

Discussion

- First study to compare ART intensification with dolutegravir in a placebo controlled randomised setting to assess virus replication while taking ART
- No differences in change to concentrations of 2-LTR circles between both treatment and placebo group
- No consistent differences in changes in marker of T-cell activation and exhaustion
- No difference in plasma makers of inflammation
- Intensification with dolutegravir did not reveal or affect virus replication
- Intensifying suppressive ART with dolutegravir does not reduce measures of immune activation
- No advantages over standard ART
- Addition of dolutegravir would only disrupt infection of new uninfected cells
- No evidence that dolutegravir can decrease the replenishment of the reservoir or hasten reservoir decay as was suggested by a previous study of raltegravir intensification

Study limitations

- The study was powered to detect a three-fold difference in the change in 2-LTR across study groups and, therefore, would not have identified minor changes below this threshold
- Only 5 individuals on PI containing ART regimen were included in the study - unable to address question of residual replication among individuals PI regimes
- All analyses were based on peripheral blood CD4 cells
- Effect on residual virus replication in lymphoid tissue cannot be ruled out
- Previous studies reported a significant effect of raltegravir leading to an increase in 2-LTR circles,
- Increase in 2-LTR circles in both of these studies was more common in participants taking PIs
- Study aimed to stratify based on PI use however number of participants taking PIs was only 12.5%,
- Probably reflects change in preferred ART regimens that are non-PI based over the past 5 years in Australia and other high-income countries

Conclusion

- No evidence that intensifying ART with dolutegravir leads to increases in the concentration of 2-LTR in peripheral blood CD4 cells in HIV-infected individuals
- Dolutegravir intensification did not lead to any changes in cell-based measures of HIV persistence, in T-cell activation, or in plasma concentrations of inflammatory biomarkers
- The addition of dolutegravir did not reveal or affect residual virus replication in blood in HIV-infected individuals on ART