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# Conference on Retroviruses and Opportunistic Infections

Making Education Easy

Virtual Meeting, 6-10 March 2021

## In this review:



**Abbreviations used in this review**

**AIDS** = acquired immunodeficiency syndrome
**ART** = antiretroviral therapy
**BMI** = body mass index
**COVID-19** = coronavirus disease 2019
**HIV** = human immunodeficiency virus
**NAFLD** = non-alcoholic fatty liver disease
**NASH** = non-alcoholic steatohepatitis
**NIAID** = National Institute of Allergy and Infectious Diseases
**PPAR-χ** = peroxisome proliferator-activated receptor gamma
**PrEP** = pre-exposure prophylaxis
**RCT** = randomised controlled trial
**SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2
**TAF** = tenofovir alafenamide
**TB** = tuberculosis
**TDF** = tenofovir disoproxil fumarate



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## Welcome to this review of the Conference on Retroviruses and Opportunistic Infections (CROI)

, a scientifically focused meeting of the world's leading researchers working to understand, prevent, and treat HIV/AIDS and its complications. The virtual approach does have advantages (I have always wished to vary the speed of some presenters; now I can) and the technology works, mostly. (Douglas Adam's aphorism that we are stuck with technology when what we really want is just stuff that works is still relevant.) The interactive Q+As remain stilted (albeit they are never particularly interactive with thousands present), and the liminal spaces are missed greatly. The content is huge, varied and exhausting to sit through. I recommend a larger screen, watching with colleagues, and plentiful snacks, coupled with a do-not-disturb sign.

Kind regards
**Dr Chris Tofield on behalf of Dr James Taylor**
christofield@researchreview.co.nz

## N'Galy-Mann Lecture: Lessons from the concurrent HIV/AIDS and COVID-19 pandemics: A two-way street

**Author:** Fauci AS

**Summary:** The HIV/AIDS pandemic and the lessons learned from this have informed the discovery and testing of innovative strategies to prevent, treat, and care for individuals with SARS-CoV-2 infection and COVID-19. The COVID-19 pandemic highlights that an effective response to the HIV/AIDS pandemic requires a novel coordinated and collaborative global effort of scientists, industry, and community partners in order to accelerate research and to ensure the implementation of science to operationalise evidence-based interventions expeditiously in real-world settings.

**Comment:** Apparently SARS CoV-2 is now classified as a retrovirus, or at least an opportunistic infection, so a large proportion of CROI was taken up with this. Tony Fauci (NIAID Director) highlighted some of the similarities between the two pandemics: the lessons learnt from HIV do seem to have been learnt by those presenting at CROI, though unfortunately not always by decision makers, to widespread frustration. Useful points were distinguishing asymptomatic and pre-symptomatic transmission (35% vs 24% of all COVID-19 cases), the HIV experience in developing vaccines (over 30 years we've found plenty of pitfalls to avoid), and how to organise RCTs. Repurposing the HIV trial infrastructure to allow rapid establishment of COVID-19 trials was repeated in multiple presentations. Denialism seemed a distant part of history, or at least pre-2020 limited to vaccination... Fauci described it as "strikingly reminiscent", and he has had a ringside seat for both.

Abstract

## Making sense of study design differences between COVID-19 platform trials

**Author:** Dodd L

**Summary:** This presentation provided a framework to evaluate study designs in COVID-19 treatment trials that are based on multi-arm platform trials allowing different experimental agents to enter and exit a study over time while sharing a control arm. Design choices that alter study rigor include endpoints, use of a placebo, use of response-adaptive randomisation, comparisons with nonconcurrent controls, the number of agents for study and when to drop or add agents.

**Comment:** An uninspiring title turned out to be great. Lori Dodd made RCT design choices come to life, particularly with trade-offs. She focussed on the issues in platform trials, in the context of a rapidly changing disease environment. This emphasised the need to ensure arms are properly matched including in time, and how to manage the updating of standard of care (do you lose the analysis of all the earlier patients?). She was also sceptical about adaptive randomisation, although I felt overly cautious. Remembering the population you sample from is the one you can (reasonably) generalise to was a handy hint, and considering the richness of evidence from the secondary endpoints is something I've never heard explicitly stated before.

Abstract

## Imaging viral life cycles

**Author:** Kräusslich H-G

**Summary:** This overview examined advances in imaging technologies that allow study of individual infection events and specific stages of the infection cycle, including high spatial and/or temporal resolution analysis of trafficking and morphological changes of individual viral components. It is now possible to visualise structural components of the extracellular virion at near atomic resolution, and gather structural information on viral components inside infected cells and their interaction with the host cell. In addition, organoid and other 3D culture systems in combination with light sheet microscopy allow analysis of virus infection in complex 3D cultures, while aspects of viral replication and spread can be studied in living animals using 2-photon-microscopy.

**Comment:** This was a title I thought I didn't understand, as obviously you can't actually watch the virus replicating. But now, incredibly, you can. This talk was packed with images of the HIV capsid moving into the cell, through the cytosol and into the nucleus. Closely watching this happen does feel a little weird; this is what's happened (or is happening if they're not fully suppressed) to all the people living with HIV that we care for. Considering the different imaging scales and what questions each can answer (i.e., *in vitro*, *in vivo*, molecular and intra-cellular, inter- and extra-cellular, organ, whole organism level) opens up new vistas.

Abstract

## HIV-1 bNAbs: Looking ahead

**Author:** Caskey M

**Summary:** This presentation discussed the results of preclinical and clinical studies of anti-HIV-1 broadly neutralising antibodies and their potential role in HIV prevention, therapy and cure. These are lab-generated monoclonal antibodies based upon natural human antibodies with high potency, which can recruit immune effector functions through Fc domains to accelerate virus clearance. In addition, they form immune complexes that are potent immunogens and can foster development of host immune responses.

**Comment:** Broadly neutralising antibodies sound like a great idea, despite the slow progress. It does seem to lack an obvious role in clinical practice though. Use as PrEP is possible, but a monthly infusion sounds time-consuming. Given the remarkable effectiveness of ART, it has a high barrier to overcome to be used as treatment, or as prevention. There may be a role as part of a cure cocktail, but maybe just using ART would be easier. The antibody resistance is already baked in, so multiple antibodies will have to be used, along with geographic variations. And finally to scale this up to be useful clinically, the cost will somehow have to fall to compare with ART, vaccines and other approaches. This is exciting science, and will continue to provide new insights, but I don't think antibody infusion clinics will start anytime soon.

Abstract

## Rifapentine +/- moxifloxacin for pulmonary tuberculosis in people with HIV

**Authors:** Pettit A et al.

**Summary:** The international, randomised, open-label, phase III non-inferiority TB Trials Consortium Study 31/ACTG A5349 examined the use of rifapentine with or without moxifloxacin in 2516 patients with drug-susceptible pulmonary TB. After adjustment for HIV status and cavitation, 4 months of rifapentine plus moxifloxacin was non-inferior (margin 6.6%) to 6 months of rifampin plus ethambutol (control) in microbiologically eligible (difference 1.0%; 95% CI -2.6 to 4.5) and assessable populations (difference 2.0%; 95% CI -1.1 to 5.1). Among 214 participants with HIV (median CD4+ count 344 cells/mm$^3$ receiving efavirenz-based ART) rifapentine plus moxifloxacin was non-inferior to control in the microbiologically eligible (difference -7.5%; 95% CI -20.8 to 6.1) and assessable populations (difference -6.6%; 95% CI -18.3 to 5.0). A favourable outcome in the assessable HIV population was observed in 91% of rifapentine plus moxifloxacin, 74% of rifapentine monotherapy, and 85% of control recipients. Fewer severe or serious adverse events occurred with the experimental regimens than the control regimen.

**Comment:** Moving to TB in HIV from COVID creates whiplash. Here investigators are trying to shorten courses from the 1970s standard, using drugs developed in the 1960s (rifapentine) and 1980s (moxifloxacin). Luckily the news is generally good, despite a moderately sick population: 4 months with rifapentine and moxifloxacin is non-inferior to a standard regimen, in both HIV and non-HIV infected populations. Regimens were all safe. ART was efavirenz-based, rather than integrase-inhibitor based. Simply swapping rifampicin for rifapentine in a 4-month regimen did not meet the non-inferiority criteria for people living with HIV. Now we just need to be able to access these drugs for our patients.

Abstract

## High dose rifampicin for HIV-associated TB meningitis: A phase II randomised trial

**Authors:** Cresswell F et al.

**Summary:** This open-label phase II pharmacokinetic trial studied the use of high-dose rifampicin (intravenous [IV] 20 mg/kg/day; oral [PO] 35 mg/kg/day) versus control (rifampicin 10 mg/kg/day) for the treatment of TB meningitis in 56 HIV co-infected African patients. Compared to control, high-dose rifampicin IV and PO increased geometric mean maximum serum concentration (6.0 vs 36.2 and 29.3 mg/L; $p < 0.001$) and area under the curve from 0-24 hours (42.9 vs 248.7 and 326.9 42.9 m×h/L; $p < 0.001$). In cerebrospinal fluid (CSF), 56% of controls had undetectable rifampicin and geometric mean CSF concentration was 0.27 compared with 1.74 and 2.17 mg/L in high-dose IV and PO recipients ($p < 0.001$). CSF rifampicin minimal inhibitory concentration (MIC) was reached in 11% of control, 93% of high-dose IV and 95% of high-dose PO recipients. No difference in grade 3-5 adverse events was observed and drug induced liver injury occurred in 1, 2 and 4 IV, PO and control recipients. 24 participants died with no difference in mortality between treatments.

**Comment:** Sticking with TB, this is a great trial looking at whether patients with TB meningitis should get higher dose rifampicin? Again this does seem something that we should already know, given sub-MIC levels of rifampicin in many patients' CSF. Reassuringly there were no more adverse effects, the increased dose led to greater than proportional increases in drug CSF levels – but no difference in patient outcomes. Phase III studies are now in progress, but there is no clinical reason to support increased dosing at present. Given the dramatic effects on rifampicin levels, I am suspicious that there is more complexity than we believe in determining outcomes.

Abstract

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## Mechanisms and treatments of steatosis in HIV

**Author:** Grinspoon S

**Summary:** NAFLD is a consequence of metabolic disease, associated with obesity, visceral adiposity and insulin resistance, and a risk factor for cardiovascular disease. Among people living with HIV, specific pathogenic factors related to increased weight, hepatic toxicities, increased visceral adiposity, proinflammatory stimuli, immune activation, insulin resistance and stimulation of critical hepatic metabolic pathways by viral envelope proteins may increase the prevalence of NAFLD. NAFLD is observed at a lower BMI in association with a greater prevalence of NASH among people living with HIV. Therapeutic strategies that target steatosis may reduce insulin resistance, or target hepatic inflammatory, immune and fibrotic pathways. Specific agents are being tested for effects on adipogenic/lipolytic pathways, including PPAR-$\chi$ agonists and stearoyl coenzyme A desaturase inhibitors, and agents with anti-fibrotic and anti-inflammatory properties.

**Comment:** The title is a little misleading, given the lack of any effective treatment beyond weight loss. There are plenty of mechanisms to target, though, and plenty of work being done to find a blockbuster drug to sell to the world (at least the bits which can afford it). Given how common NAFLD is, particularly in countries with high rates of obesity (that's us!), we probably should be more aware and more concerned about it. This is particularly pertinent with the rapid changes seen with integrase inhibitors, and the increased rates of NAFLD for a given BMI in HIV-positive people. It is possible this is related to the rapidity of the weight gain, rapid weight gain being more likely to cause steatosis (and type 2 diabetes mellitus). We do seem to be inching towards an acceptance that driving a reduced intake is the easiest way to improve these issues; changing the environment back to a less obesogenic one will take ongoing hard work.

Abstract

## Panel discussion: Case based discussion on weight gain in HIV and antiretroviral therapy

**Panel:**

Grace McComsey, University Hospitals Cleveland Medical Center; USA

Sadaf Farooqi, Cambridge University; UK

Jane O'Halloran, Washington University in St Louis, USA

Cissy Kityo, Joint Clinical Research Centre, Uganda

**Summary/Comment:** This topic continues to provide discussion, although we are moving towards some consensus. Second-generation integrase inhibitors do cause weight gain in some people; TDF (but not TAF) seems to prevent weight gain, and return to health can be both dramatic ("the consumption of energy by a roaring immune system can be significant" was explained to us by the endocrinologist on the panel, perhaps unnecessarily) and overshoot baseline (healthy) weight. The differential effects between TDF and TAF may potentially be related to mitochondrial toxicity, given much lower levels of TAF. The "overshoot" has been demonstrated in starving healthy volunteers; whether this biological phenomenon applies to recovering from acute illness is unclear, or if the weight gain seen is more socially mediated.



## Single vascular cell heterogeneity in health and disease: A COVID-19 update

**Author:** Carmeliet P

**Summary:** This paper discussed endothelial cell biology and the postulate that they are essential contributors to the initiation and propagation of severe COVID-19 by altering vessel barrier integrity, inducing a pro-coagulative state and vascular inflammation, and mediating inflammatory cell infiltration. It also focuses on heterogeneity between and within vascular beds and their divergent global and metabolic characteristics and the specific functions of endothelial cell subtypes. It also discusses the link between endothelial cells, viral infection and inflammatory changes.

**Comment:** The endothelium seems to be a magical wand, with which all human health and disease can be explained, much like the microbiome, or the genome (back in the early 2000s anyway). The basic science, as explored here, does show many potential targets and provides explanations for the variation in disease between individuals. Whether this can translate into treatments is more dubious. This is a prime example of a question worth exploring, but prior to the pandemic, rarely studied due to difficulties of having enough patients at the same site within a reasonable time frame. In 2020 this was not a problem.

Abstract

## Sustained delivery and long-acting agents for prevention of HIV

**Author:** Bekker L-G

**Summary:** For many reasons, daily oral PrEP is not always feasible in all individuals and settings. Long-acting PrEP agents may provide an expanded range of options. This paper gave an overview of long-acting agents, efficacy and safety profiles, advantages and disadvantages and mitigation of challenges.

**Comment:** Linda-Gail Bekker enthused her way through this with a quick summary of why daily PrEP isn't great (humans aren't good at making good daily decisions that maintain the status quo, i.e., remain uninfected), before moving onto what options are coming. Essentially there are lots, with intramuscular injections, vaginal rings, monthly oral pills, long-acting implants and broadly neutralising antibodies (see above). She finished with a quick view of the advantages and questions remaining (pharmacokinetics, stopping/starting; service set up). I was left feeling in favour of good things, though infectious disease services still don't seem best placed to run preventative services.

Abstract

### Independent commentary by Dr James Taylor MB ChB (Aberdeen), FRACP

Dr Taylor is a consultant in infectious diseases and general medicine at Capital and Coast DHB. James is currently on parental leave, and looking forward to returning to work for a rest.



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