PredART trial shows prednisone is safe and effective for preventing TB-IRIS

The findings of the PredART trial were presented at the annual Conference on Retroviruses and Opportunistic Infections (CROI) that took place in Seattle, United States, from 13-16 February 2017. This trial is the first to demonstrate the efficacy and safety of prednisone for preventing the tuberculosis-associated immune reconstitution inflammatory syndrome (TB-IRIS) in patients at high risk for this condition.

The trial was conducted as a collaboration between investigators from UCT, Imperial College London and the Institute of Tropical Medicine in Belgium. UCT investigators included **Graeme Meintjes** (Principal Investigator; CIDRI & Member of the IDM), **Robert J. Wilkinson**, **Gary Maartens**, Cari Stek, Liz Blumenthal, Friedrich Thienemann and Charlotte Schutz. The main funder of the trial was the the European and Developing Countries Clinical Trials Partnership (EDCTP), with co-funding received from the South African National Department of Science and Technology and the Wellcome Trust.

TB-IRIS is the most frequent complication of starting antiretroviral therapy in patients with advanced HIV being treated for active TB disease (it affects up to 50% of such patients). It manifests with recurrent or new inflammatory features of TB during the first few weeks of ART resulting in clinical deterioration frequently necessitating hospital admission. Patients complain of recurrence of their TB symptoms, and may develop enlarging lymph glands in their neck, TB abscesses or worsening of their chest X-rays.

The trial was conducted at Site B clinic in Khayelitsha at the Clinical Infectious Diseases Research Initiative (CIDRI) clinical research facility. It was a randomized, double-blind, placebo-controlled trial: 240 patients who were HIV-infected with a CD4 T-cell count of 100 cells/mm^3 or lower, who had never received ART previously and were recently diagnosed with TB disease were enrolled. All participants received TB treatment and ART. Participants were randomized in a 1:1 ratio to receive prednisone for 4 weeks or identical placebo for 4 weeks started at the same time as their ART medication, and followed intensively for a further 8 weeks. A moderate dose of prednisone was used: 40mg per day for 2 weeks followed by 20mg per day for 2 weeks. Prednisone is a corticosteroid anti-inflammatory drug that is widely used for the treatment of conditions such as asthma and certain forms of arthritis.

The primary comparison was the proportion of participants who were diagnosed with TB-IRIS. In participants who received prednisone there was a significant (30%) relative reduction in the risk of developing TB-IRIS: 46.7% of patients in the placebo arm developed TB-IRIS compared with 32.5% in the prednisone arm. There was a trend towards fewer hospital admissions in the prednisone-treated participants.

Also important is that prednisone appeared to be safe in these patients with advanced HIV. Adverse events and severe infections were not more common in the prednisone-treated participants. One case of Kaposi's sarcoma (an HIV-related cancer) occurred: this was in a patient in the placebo arm who stopped taking ART.

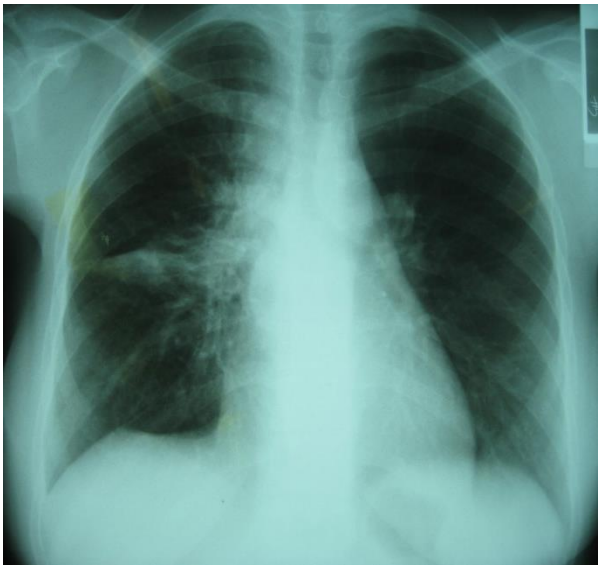
Prednisone is a cheap and readily accessible drug in developing world settings. In this trial, it was demonstrated that it reduces the incidence of TB-IRIS by 30% in patients on TB treatment at high risk for TB-IRIS starting ART. It was also safe. These findings provide the first evidence of an effective strategy for reducing the risk of developing TB-IRIS which is a very common early complication of ART in South Africa.

Links:
CROI presentation:
http://www.croiwebcasts.org/console/player/33484?mediaType=slideVideo&
CROI press conference:
http://www.croiwebcasts.org/console/player/33488?mediaType=slideVideo&
Short film about PredART trial made in 2015 by EDCTP:
https://www.youtube.com/watch?v=BvnxfpWBsFU
PredART website:
https://www.predart.org/site/index

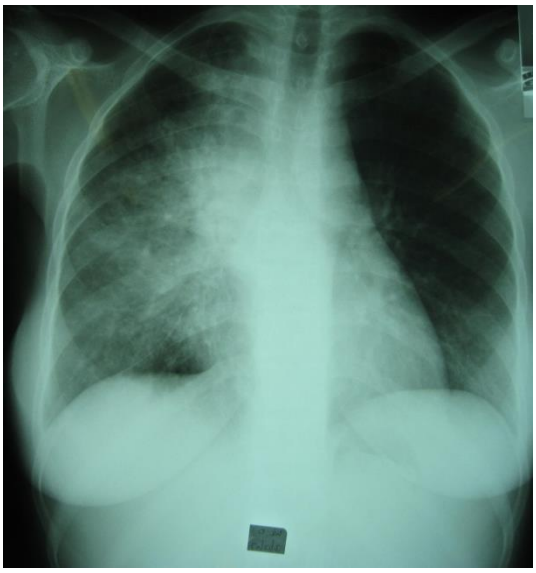
PredART
Investigating TB-IRIS Prevention

PredART trial clinical team meeting at Site B clinic in Khayelitsha where the trial was conducted

1)



2)



Chest X-ray worsening due to TB-IRIS: the first X-ray was taken prior to ART, the second when the patient presented with TB-IRIS.