Third Conference on Antiretroviral Drug Optimization (CADO 3)

Summary Meeting Report

29 Nov-01 Dec 2017

Rosebank Crowne Plaza, Johannesburg, South Africa

Background and objectives: The *Third Conference on Antiretroviral Drug Optimization (*CADO 3) was held at the end of 2017. The meeting's objective was to define the critical research necessary to optimize second- and third-line antiretroviral treatment (ART) regimens for adults and the sequencing and recycling of key products in a public health setting: tenofovir prodrugs (tenofovir disoproxil fumarate [TDF] and tenofovir alafenamide [TAF]), dolutegravir (DTG), and darunavir/ritonavir (DRV/r).

The discussions were undertaken in the context of what will likely be the first-line standard of care in five years' time (i.e. transition to DTG and TAF). The workshop also addressed the need to ensure that products would be safe and effective in populations in low- and middle-income countries including: pregnant and breastfeeding women, people with TB and other comorbidities, people with HIV drug-resistant strains, and under conditions where disease monitoring is insufficient or contact with health services is infrequent.

Number of participants: Approximately 70 experts attended the conference, including academia, non-governmental organizations, country programme managers, regulatory agencies, donors and community representatives (see annex 1).

Overview of the methodology: The workshop included three session topics: (1) sequencing and recycling, (2) treatment monitoring and maintenance regimens, and (3) planning for the future. Session topic co-chairs shared background materials and desired outcomes in advance of the workshop. Each session was structured to summarize current knowledge and then debate and find agreement on what is known, what are the key unknowns, and what essential research opportunities will be needed to advance the treatment of people living with HIV in a public health setting (see annex 2). The participants completed a questionnaire addressing the key issues at the end of each session and the results were compiled (see annex 3).

Expected outputs: The workshop organizers plan to summarize opinions on DTG, define a list of priority research questions related to ART optimization, and share a prioritized portfolio of key adult ARV products and their associated formulations that should be developed by manufacturers.

Key points discussed and conclusions: The growing evidence provided by programme data on the safety of DTG in first-line, particularly from Botswana, Brazil and small European cohorts was discussed and supports DTG's further expansion as the preferred first-line option. The participants noted that this drug should not be viewed as a "magic bullet" to solve adherence problems and that its role as a substitution for stable patients on an efavirenz-based (EFV) regimens and in second-line is still debatable. Low dose EFV was viewed as the alternative first-line option for those who cannot tolerate DTG or where it cannot be accessed because of intellectual property (IP) issues or cost. The workshop does not support the use of two-drug combination regimens for adults (e.g., DTG/RIL, DTG/DRV/r, DTG/3TC, DRV/r/3TC) given current clinical trial data. Recent and ongoing simplification studies using this approach have not considered the LMIC context and are therefore missing important populations (e.g., pregnant women, TB and HBV co-infections) as well as the substantial

programmatic challenges. As such, significant additional clinical research is needed before two-drug combination regimens can be reconsidered.

A prioritized list of research questions was established (see Figure 1). Clinical studies on sequencing and recycling of TDF and TAF as well as on the role of DTG in patients who previously failed NNRTI-containing regimens were defined as key priorities. A heat-stable, boosted protease inhibitor formulation of DRV/r is expected to be available in 2018. The workshop viewed this as an excellent opportunity to transition to DRV/r as the preferred option for second-line in the near future assuming it is priced similar to lopinavir/ritonavir. Dose optimization studies on use of low dose DRV/r in second-line for patients who either failed a first-line regimen or were stable on an alternative second-line regimen was elected as a medium term priority.

Use of oral and injecting long acting drugs as well as nano-formulations and implantable devices were viewed as high-priority opportunities and investment in their development should be continued over the longer term. Furthermore, in order for these studies to be relevant to HIV positive people in LMIC, all clinical work should include pregnant and women of child-bearing age, adolescents, patients coinfected with TB and on treatment, and other co-morbidities. To ensure programmatic issues are adequately addressed this work should also include community participation, full access to necessary IP, and product development and commercialization incentives.

Figure 1: list of research questions

Clinical studies on sequencing and recycling of TDF and TAF

- Switching from TDF to AZT (SoC) versus maintaining TDF in second-line after failing a TDF regimen in first-line
- Retrospective resistance testing

Clinical studies on use of DTG in second-line patients who failed to EFV vs 2 NRTI + PI (SoC)

- Consider factorial on NRTIs use
- Clinical data to support whether DTG boosting is necessary for rifampicin containing co-administration (in HIV/TB patients)
- If programmes start implementation before clinical trial results: enhanced monitoring protocol and only proceed if good access to viral load monitoring; organize result monitoring to gather real data

Dose optimization study on use of low dose DRV/r in second-line patients

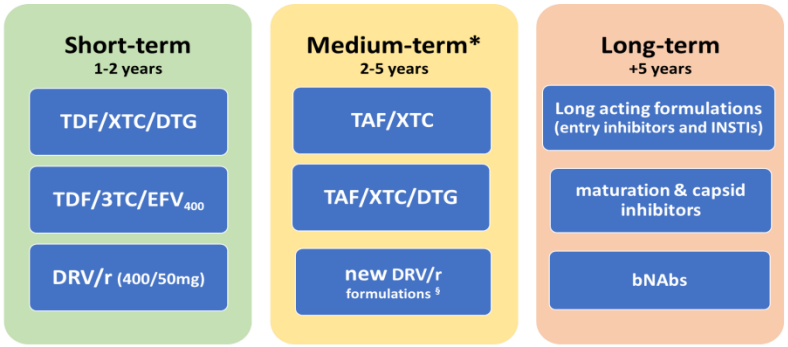
- DRV/r 400/100mg OD versus DRV 800/100mg OD (SoC)
- Consider factorial on NRTIs used

All studies should reflect real characteristics of people in treatment programmes (e.g. pregnant & women of child-bearing age, TB co-infection and other co-morbidities)

- Include community participation and development incentives

A prioritized portfolio of new adult ARV products that accounted for trends in ARV optimization was defined (see Figure 2). This product portfolio will be updated on a regular basis, similar to the PADO list, as new information is made public on existing products in the portfolio or on new products.

Figure 2: list of prioritized optimized products and formulations for use in adults living with HIV



* Other lower priority products might be considered in the future if new data suggests superiority to existing priorities
§ Low dose standard formulation (400/100mg) or standard dose nanoformulation (800/100 mg)

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