The potential clinical impact of the observed differences in IL-6, a marker of inflammation, associated with some antiretroviral regimens

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Introduction (1 of 3)

- Guidelines recommend a variety of two- or three-drug antiretroviral (ARV) regimens (2DRs/3DRs) for treating people living with HIV (PLWH)[1,2]
  - Although guideline-recommended 2DRs and 3DRs are virologically effective, further information is warranted about possible differentiating factors
- In some instances, inflammatory markers, including interleukin-6 (IL-6), differ among some oral 2DRs and 3DRs[3–5] (**Table 1**)

Table 1. IL-6 Levels in 2DRs and 3DRs in the TANGO and SALSA Studies

Study	Switch	Change in IL-6 level after switching from 3DR to 2DR
TANGO	Switch to DTG/3TC vs. continuing a TAF-based regimen	Week 48: Statistically significant difference favoring 3DR ($P = 0.006$)[3] Week 96: Numerical difference but not statistically significant[4] Week 144: Statistically significant difference favoring 3DR ($P = 0.039$)[5]
SALSA	Switch to DTG/3TC vs. continuing a variety of 3DRs	No difference over 48 weeks of treatment[6]

Introduction (2 of 3)

- In the AIR study, significant differences between oral 2 and 3DR in IL-6 levels, favoring lower levels on 3DR, increased over years[7] (**Figure 1**)
  - Similar findings were seen with D-dimer and C-reactive protein
- Changes in inflammatory markers may depend on the antiretrovirals used[8,9]
  - SALSA included changes from multiple third agents to DTG which may reduce IL-6 levels[11], as well as changes from a 3DR to a 2DR, which may increase IL-6 levels
  - These opposing directions of change may have contributed to the observed results

Figure 1. Effect of Switching From a 3DR to 2DR on Serum IL-6 Levels in the AIR Study[7]

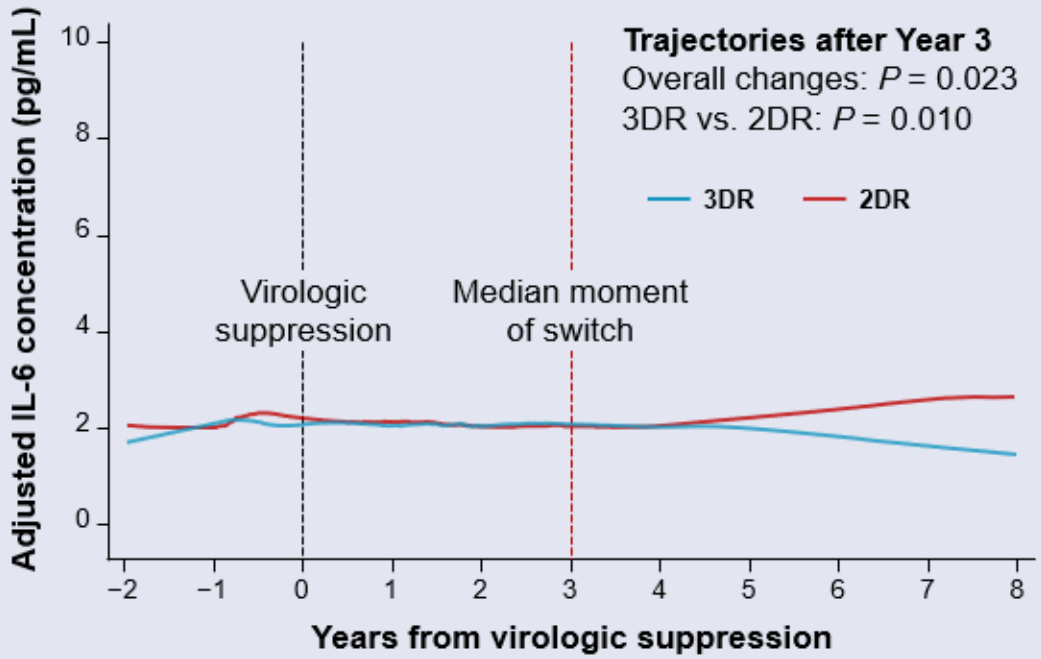


Image adapted from Serrano-Villar S, et al. AIDS 2020;OAB0304 (slide presentation)

Introduction (3 of 3)

- Previous analysis of PLWH on suppressive oral ART in three studies performed by the INSIGHT trials network showed that elevated inflammatory markers, in particular IL-6 and D-dimer, are associated with a higher risk of serious non-AIDS events (SNAEs: cardiovascular, hepatic or renal event, malignancy) and death[10]
  - Modelling[10] predicts that a 16% increase in IL-6 level may increase the risk of SNA/death by about 16% (**Figure 2**)
    - TANGO week 48[3] reported a 16% difference in IL-6 between the arms favoring 3DR

Figure 2. Estimated Reduction in Risk of SNAE/Death Associated With Decreasing Levels of IL-6 and D-Dimer*

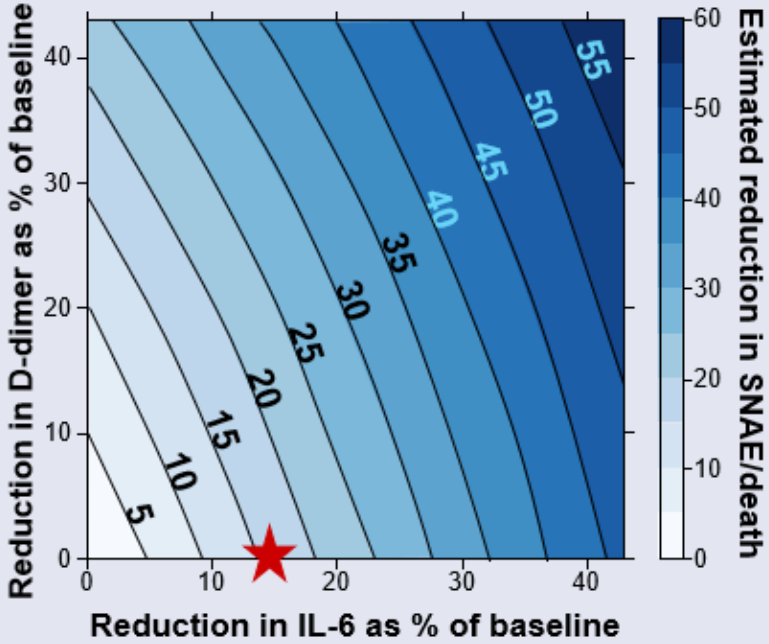


Figure adapted from Grund B, et al. PLoS One 2016;11:e0155100. Distributed under the terms of the CC BY 4.0 license

Aims

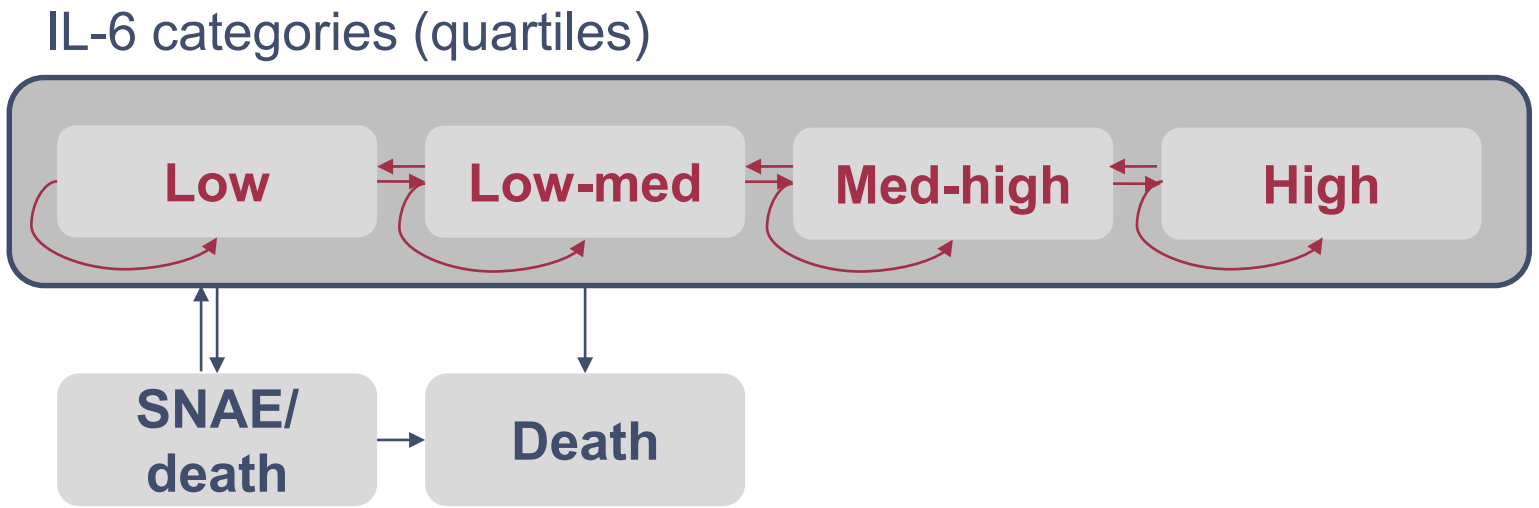
- To mathematically model whether the differences in IL-6 levels associated with remaining on a 3DR, versus switching to a regimen with a higher IL-6, as seen with data from some current oral 2DRs, may affect clinical outcomes (SNAE/death) in virologically suppressed PLWH
  - The model inputs for IL-6 differences uses data from the TANGO and AIR studies

Methods (1 of 4)

- A Markov model was created using observed differences of higher IL-6 levels in the TANGO[3] and AIR[6] studies in virologically suppressed PLWH switching from a 3DR to a 2DR
  - We developed a model based on observed variation in IL-6 (trajectories over time)
  - The model used TANGO data for the first 3 years and AIR data for > 3 years
    - This is updated from the model reported in our abstract, which did not have access to TANGO data after week 48
  - At entry in the model, age was set at 39 years[10] and baseline IL-6 levels were divided by quartiles based on the distribution in the AIR study[7] cohort
  - The model output was based on published analyses from the INSIGHT trials network, which defined the predicted change in risk of SNAE/death by changes in IL-6 concentration based on data from 3,766 individuals from the virologically suppressed arms of the SMART, ESPRIT and SILCAAT studies[10]

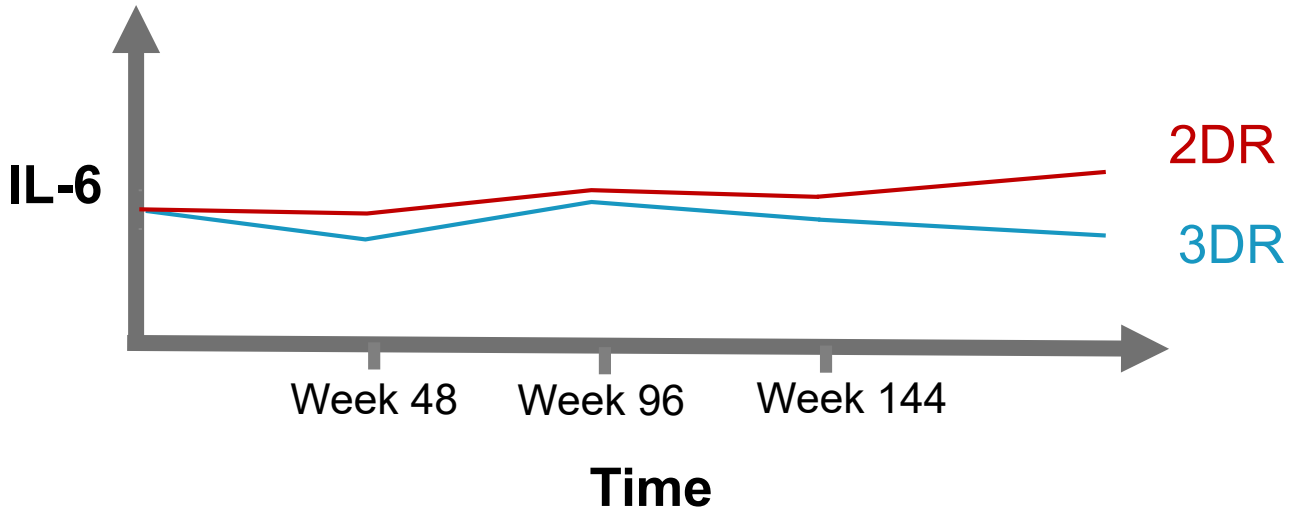
Methods (2 of 4)

Markov modelling provides a standard framework for predicting clinical outcomes in terms of transitions between states based on the current state occupied by an individual. Per year, an individual can cycle through the model with no events, a SNAE, and/or death



Methods (3 of 4)

Approximate time course of changes in IL-6 concentration that went into the Markov model (based on changes in IL-6 seen in TANGO Week 48, 96, 144 and AIR data)



Note: Graph is illustrative only of the overall trends inputted into the model, and not intended to reflect the exact data points that were inputted

Methods (4 of 4)

- **The primary endpoint of our study was the number needed to treat (NNT) that the model predicts would result in one additional SNAE/death based on the observed changes to IL-6**
- We also estimated the size of a clinical cohort, including a randomized clinical trial, that would be needed to support or refute this effect

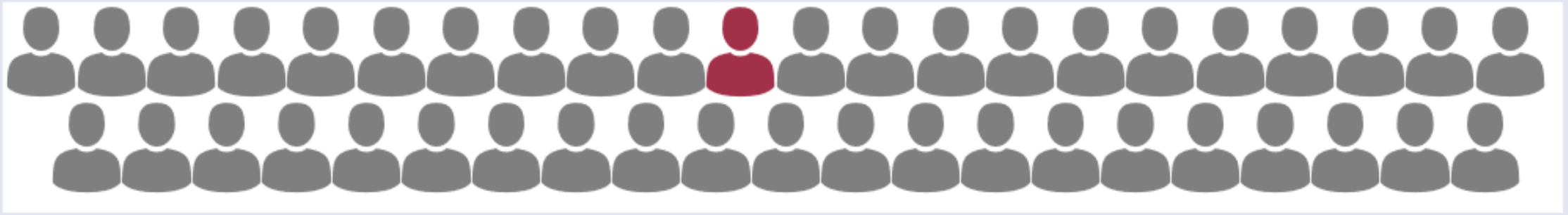
Results

- PLWH maintained on a 3DR spend 22% more time in the "low" IL-6 quartile
- Those on a 2DR spend 16% more time in the "high" IL-6 category
- As a result, the mean number of SNAE/death events that are expected to occur for every 100 PLWH over 144 weeks was 5.6 (3DR) vs 6.8 (2DR)

Results: Number Needed to Treat (NNT)

- Based on the model, for every 43 PLWH 30–50 years old treated for 5 years with a regimen associated with higher IL-6, there would be one additional SNAE/death outcome (**Figure 3**)

Figure 3. NNT to Observe One Additional SNA/Death Outcome After the Switch From a 3DR to a 2DR Based on the Observed Higher IL-6 Levels With 2DRs in PLWH Aged 30–50 Years and Receiving 5 Years of Treatment: NNT=43



NNT of 43: for every 43 PLWH treated with a regimen that has a higher IL-6 for five years, the model predicts there would be one additional SNA/death event

Results

- The NNT varies with years on treatment (**Table 2**)

Table 2. NNT to Observe One Additional SNA/Death Outcome on a 2DR vs. 3DR by Time on ART, Based on the Observed Higher IL-6 Levels With 2DRs

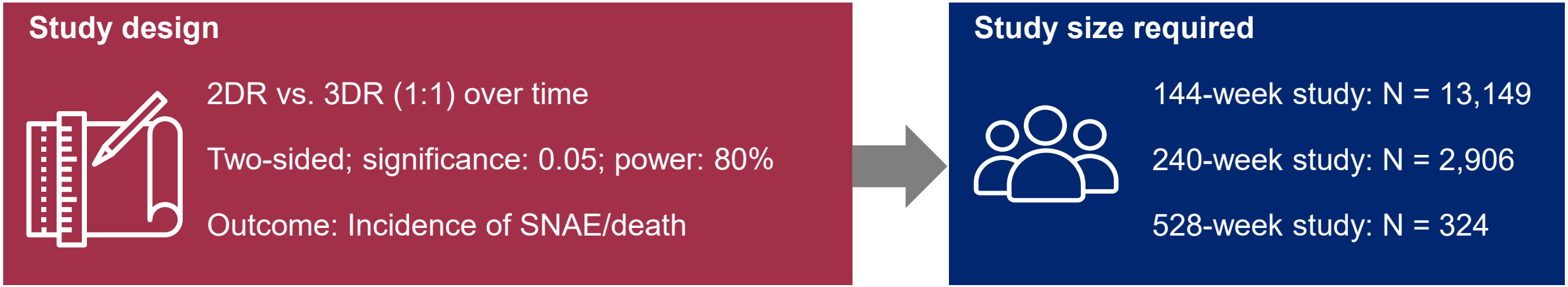
Time (years)	NNT
3	106
5	43
10	13

Estimates from Markov modeling considered participant age range of 30-50 years

Results

- Given that these model data suggest an important clinical impact of the elevated IL-6 levels, we estimated the cohort size required to support or refute an effect of this magnitude (**Figure 4**)

Figure 4. Clinical Study Design and Study Size Required to Test the Hypothesis



- Note: If unequal sample sizes were used in the study (i.e., not 1:1), then different study sizes are required. For example, for a study including 9,000 PLWH taking a 3DR over 144 weeks, the distribution of patients would need to be about 2:1, i.e., around 5,000 PLWH taking 2DR would need to be included in the study to achieve a power of 0.8.

Limitations

- Only changes to IL-6 were modeled
- These results are not generalizable beyond the ARV regimens studied in TANGO and AIR
  - More recent two drug regimens, e.g., long acting injectables, have longer half-lives and other differences which may affect the risk of inflammation over time
- While guidelines[1,2] acknowledge the importance of inflammation in PLWH, they cannot provide specific recommendations for the measurement, prevention or treatment of inflammation given a lack of adequately powered trials which address this question

Guidelines

- Current guidelines on inflammation are summarized in **Table 3**

Table 3. International Guidelines on Inflammation and Immune activation

DHHS 2021[1]	EACS 2020[2]
"Persistently low CD4 cell counts and immune activation are each associated with increased AIDS- and non–AIDS-related morbidity and mortality among individuals with ART-mediated viral suppression"	"Potential contributors to comorbidity pathogenesis include a higher prevalence of recognised risk factors, potential toxicities from ART exposure, and HIV infection (or coinfections with CMV and HCV) contributing to immune dysfunction/dysregulation, chronic immune activation and inflammation"
"Interventions designed to increase CD4 cell counts and/or decrease immune activation are not recommended outside of a clinical trial, because no current interventions have been proven to decrease morbidity or mortality during ART-mediated viral suppression"	"CD4/CD8 ratio is a stronger predictor of serious outcomes vs. CD4 count"

Conclusions

- Over the long term, higher inflammation may negatively impact clinical outcomes for PLWH
- Levels of inflammatory markers, including IL-6, have been reported to differ after a switch between antiviral classes as well as from some current 3DRs to some current oral 2DRs
- Our Markov model suggests that the IL-6 elevation observed with the switch from some 3DRs to some 2DRs may increase the risk of serious non-AIDS events and/or death in PLWH
  - The IL-6 differences observed with the switch would be expected to result in one additional SNAE/death event for every 43 people (age 30-50) treated for 5 years
  - Further studies are warranted to confirm the observed differences
    - If confirmed, long-term clinical studies may help optimize care given the concerns raised here
    - A 240-week study with approximately 2900 participants would be required to evaluate this clinically

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