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## BACKGROUND

• Shorter TB regimens are a WHO priority, but visible cutaneous adverse effects may affect acceptability.

• Clofazimine is attractive for treatment shortening but is associated with skin discoloration. Mechanism of skin discoloration is unknown, may be 1) associated with deposition of drug-related crystals, 2) due to increased photosensitivity, or a combination of these hypothesized mechanisms.

• Prior studies rarely objectively quantify magnitude or the time course of clofazimine-induced skin color change.

## METHODS

### Design and participants:

CLO-FAST randomized adults with drug-susceptible TB 2:1 to:  
 • CLZ+ arm (13-week isoniazid, rifapentine, pyrazinamide, ethambutol, and clofazimine with 2-week loading dose)  
 • CLZ- arm (26-week standard isoniazid, pyrazinamide, rifampicin and ethambutol)

### Assessment schedule

Skin color assessed at **baseline** and **weeks 8, 13, 26, and 65** using:

- Objective colorimetry (CL-400 Courage+Khazaka) at inner upper arm and four facial sites
- Participant self-assessment (0-10 of perceived color change)

### Colorimeter data processing and analysis

At each measurement site, CIELAB color space coordinates  $L^*$  (luminosity),  $a^*$  (green-red axis) and  $b^*$  (blue-yellow) were recorded in triplicate and the median was used for analysis.

**Pigmentation index:** individual typology angle (ITA), an established surrogate for melanin-associated pigmentation:

$$ITA = \tan^{-1} \left( \frac{L^* - 50}{b^*} \right) * \frac{180}{\pi}$$

**Primary objective endpoint:** color difference from baseline  $\Delta E$ :

$$\Delta E = \sqrt{(L^* - L_0^*)^2 + (a^* - a_0^*)^2 + (b^* - b_0^*)^2}$$

Higher  $\Delta E$  values indicate greater degree of perceived color difference:

$\Delta E > 2$  is threshold of perceptibility

$\Delta E > 5$  is clearly distinguishable

### Comparisons

Primary between-arm comparison was at each regimen's end of treatment (week 13 for CLZ+, week 26 for CLZ-) with longitudinal follow-up through week 65.

In CLO-FAST, the 3-month clofazimine-containing DS-TB regimen caused greater, often perceivable skin color change at end of treatment versus standard therapy, without pigmentation-related discontinuations, and with substantial reversal after treatment.

## RESULTS

- 55 participants in CLZ+ group, 30 participants in CLZ- group, overall median age 33 (IQR 26–39), 22% female
- Most with baseline pigmentation ranging from brown to very dark (Figure 1)
  - Inner arm ITA median [IQR] CLZ+ vs CLZ-: -35.4 [-42.8, -26.0] vs -27.7 [-33.9, -17.4]
  - Face ITA median [IQR] CLZ+ vs CLZ-: -46.4 [-53.6, -38.8] vs -42.5 [-48.7, -30.1]

### Objective colorimetry (Figure 2-3):

- Greater decrease in  $L^*$  and  $b^*$  (face+arm) and  $a^*$  (face) in CLZ+ vs CLZ- at end of treatment (EOT)
- More perceivable color change ( $\Delta E$ ) in CLZ+ than CLZ- at end of treatment (EOT)
  - Inner arm: median  $\Delta E$  5.3 vs 3.7 ( $p=0.002$ ); Face: median  $\Delta E$  5.0 vs 3.4 ( $p<0.001$ )
  - Perceivable change ( $\Delta E > 5$ ) at end of treatment: arm 55% vs 23%; face 51% vs 14%

### Self-assessment (Figure 4):

- End of treatment: non-zero distress 33% vs 2% (CLZ+ vs CLZ-)
- Week 65: distress uncommon (6% vs 8%) and  $\Delta E$  differences no longer significant

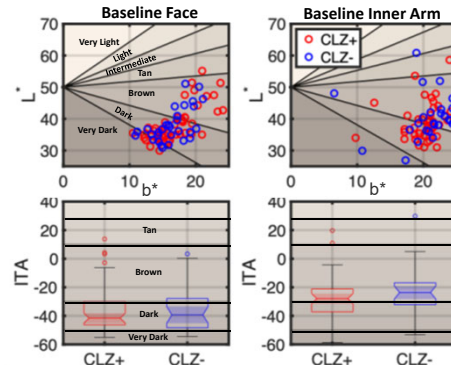


Figure 1. Baseline  $L^*$  vs  $b^*$  coordinates (upper panel) and ITA boxplot comparison (lower panels) between CLZ+ and CLZ- groups for face (left panels) and inner arm (right panels). Each plot is shaded by regions of ITA ranging from very light (>55°) to very dark (<50°).

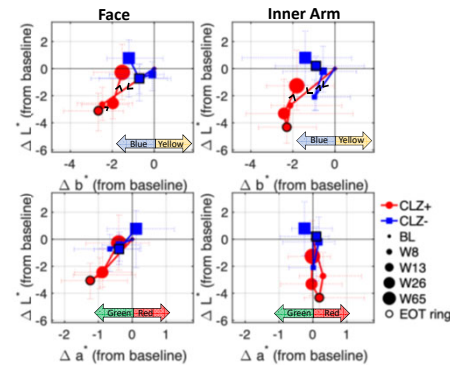


Figure 2. Changes in  $L^*$ ,  $a^*$ , and  $b^*$  coordinates across study timepoints (increased marker diameter) relative to baseline (BL) for CLZ+ and CLZ- groups for face (left panels) and inner arm (right panels). Black arrows in upper panel emphasize timepoint progression, black outline indicates end of treatment (EOT) for each arm.

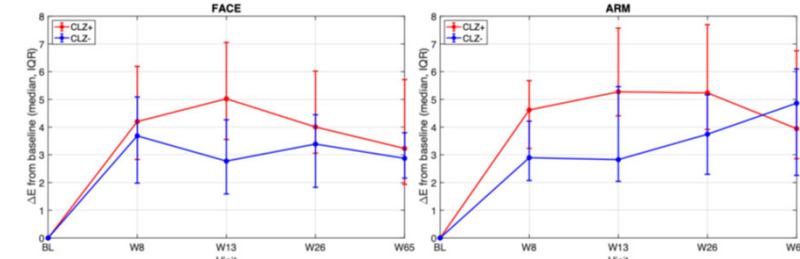


Figure 3. Colorimeter-determined color-difference  $\Delta E$  relative to baseline (BL) across study timepoints (W8-65 = weeks 8 through 65) for CLZ+ and CLZ- groups for face and arm.

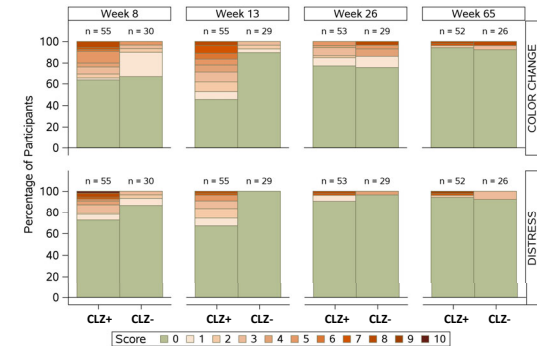


Figure 4. Summary of scores across study timepoints for both CLZ+ and CLZ- groups for participant self-assessment of (top panel) change in skin coloration since start of TB treatment, and (bottom panel) distress caused by change in skin coloration since start of TB treatment. Score of 0 indicates no color change or distress.

## CONCLUSIONS

- A 3-month clofazimine-containing regimen produced larger, often perceivable skin color changes at end of treatment vs standard therapy.
- Objective colorimetry and participant-reported outcomes are concordant over time, with resolution after treatment.
- Pigmentation change occurred along color space axis consistent with melanin-associated hyperpigmentation, not consistent with increased redness from crystal deposition.
- Pigmentation changes were tolerated: no discontinuations attributed to skin color change; persistent distress was uncommon.

Implications: Quantitative, perceptibility-based measures ( $\Delta E$ ) can support objective regimen evaluation. Assessment of changes in color space coordinates may provide insights into the mechanism of perceived color change.

## ADDITIONAL KEY INFORMATION

The authors thank the participants, sites, and investigators in the NIH DAIDS ACTG trial network (award UM1A1068634, UM1A1068636, UM1A106701).

## PLAIN LANGUAGE SUMMARY

People taking the 3-month regimen that included clofazimine had more noticeable skin darkening during treatment than those on standard therapy. For most participants, distress was low and skin color changes improved after treatment ended.