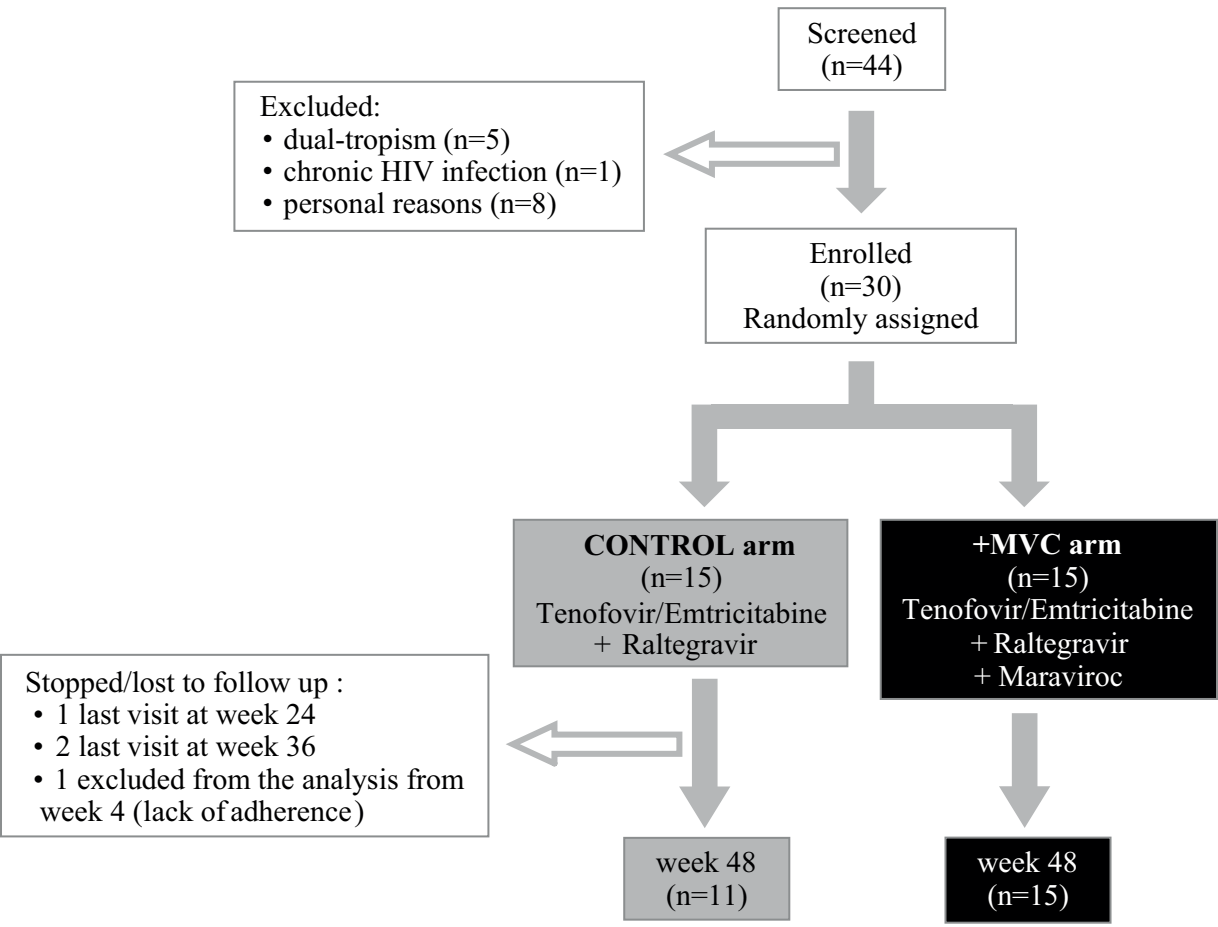Supplemental Digital Content 1. Study Flow chart