Implementation of an Online Drug-Drug Interaction Screener for STRIVE Ensitrelvir Trial for COVID

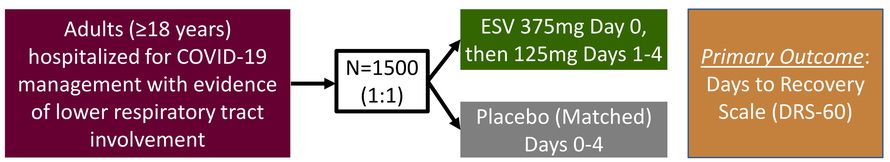
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Background

- Ensitrelvir (ESV) is an investigational, oral protease inhibitor for SARS-CoV-2 infection
- ESV is associated with drug-drug interactions (DDI) due to inhibition of cytochrome P450 (CYP) 3A, P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporter-3 (OAT-3)
- ESV exhibits a ~48-hour half-life presenting DDI potential for ~10 days after last dose
- ESV is currently being studied in a randomized, placebo-controlled trial of patients hospitalized for COVID-19 with the STRIVE (Strategies and Treatments for Respiratory Infections and Viral Treatments) network; a global research network with >200 study sites across 28 countries
- STRIVE-1 ESV Trial:



- STRIVE-1 ESV Trial leadership assembled a multidisciplinary team to address ESV DDI management and provide trial sites with DDI resources.
- The STRIVE-1 ESV DDI team developed an online, DDI screener for STRIVE-1 ESV trial conduct (https://www.insight-trials.org/DDI/). The STRIVE DDI Screener went live in December 2022, and the first enrolled participant was in February 2023.

Methods

- A database of commonly used medications was initially compiled to assess for DDI with ESV based on drug metabolism characteristics
- Medications were classified for use with ESV within 3 categories:
  - **Permitted**
  - **Conditionally Permitted**: permitted with dose modification; dose reduction or maximum threshold
  - **Prohibited**
- Conditionally Permitted and Prohibited medications during trial conduct were assigned the following guidance:
  - **Wash-out Period**: recommended time between last interacting medicine and ESV initiation; Conditionally Permitted medications
  - **Restart/Start Timeline**: time between when an interacting medication can be restarted or started relative to the ESV treatment course
  - **Additional Guidance**: includes additional clinical guidance recommendations and permitted alternative medications if applicable
- The trial DDI database is being updated regularly and uploaded to the online portal
- Version updates of the STRIVE DDI Screener were completed iteratively through V6
- Additional DDI resources were developed to help guide sites with DDI management during the trial including a 2-sided DDI quick reference sheet (A-Side, trial DDI categorization of commonly used medications; B-Side, guidance on emergency use medications), protocol instruction manual, and discharge materials

Results

- Version 1 of the STRIVE DDI Screener included 615 medications
- Five version updates have been completed resulting in 1117 medications included in V6 of the DDI screener (**Figure 1**)
  - Mean number of changes per screener version: 102
- Details of Version 6 of the STRIVE DDI Screener:
  - 67% of medications permitted
  - 32% of medications prohibited
  - 1% (n=11) of medications conditionally permitted
    - From calcium channel blocker, macrolide, antidepressant classes
    - Dosage reduction guidance in 5 (45%)
    - Maximum dosage limits in 6 (55%)
- As of January 10, 2024, 230 participants have been enrolled, and a total of 76,875 medication searches were conducted
- Top searched medications were from the antihypertensive, antibiotic, and anticoagulant, and corticosteroid classes (**Figures 2-3**)
- Due to trial blinding considerations, anticoagulant, transplant immunosuppressants, and emergency use medications posed the greatest guidance challenges

Figure 1. Total medications included in STRIVE DDI Screener by version

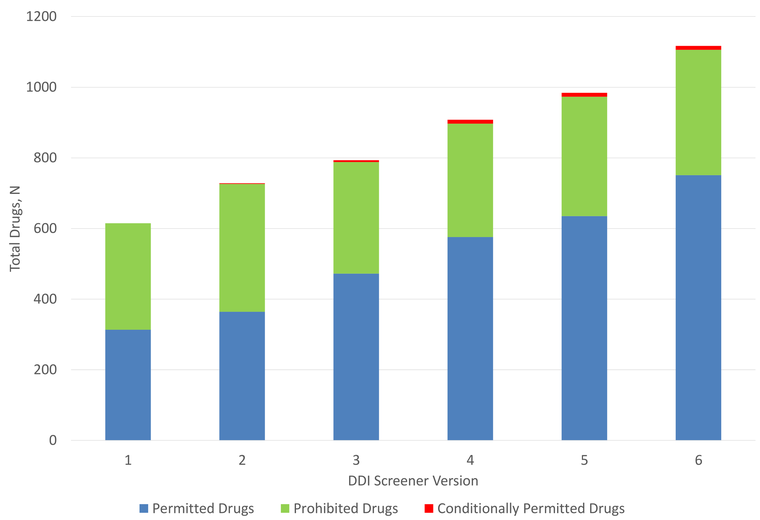


Figure 2. Top 10 medications searched in STRIVE DDI Screener

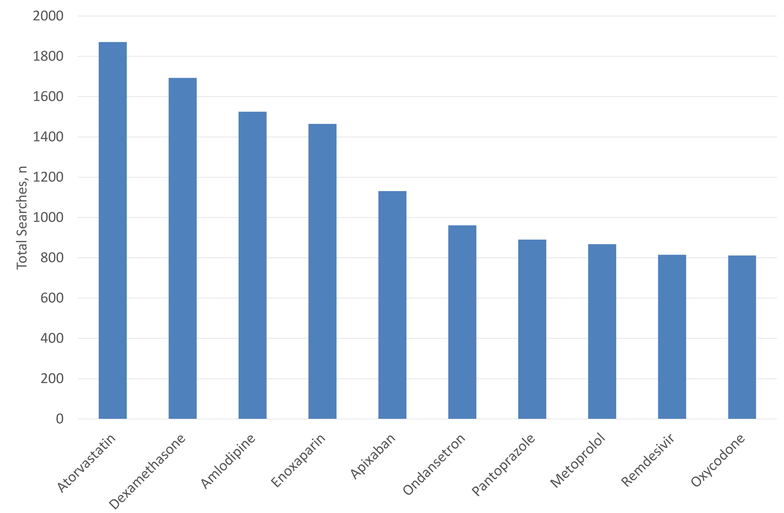
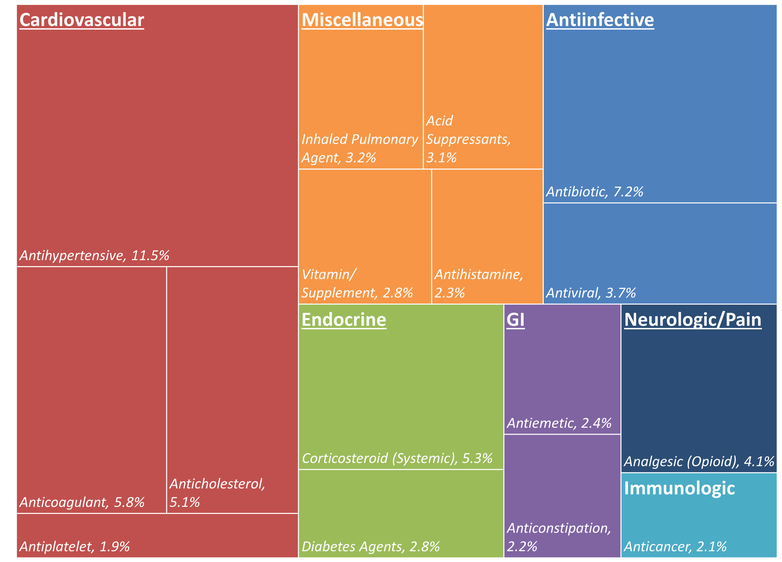


Figure 3. Top medication classes searched in STRIVE DDI Screener



Conclusions

To our knowledge, this is the first online interactive DDI management tool developed for a placebo-controlled trial of investigational agents. DDI resources for drugs like ESV with a high DDI potential are essential for safe clinical trial conduct. Based on usage data and informal feedback, this online screener meets this need for trial sites. Implementation requires a multidisciplinary and iterative approach to add new data as available and allow feedback from study sites. Concomitant medication dose adjustments require careful consideration to protect blinding.

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