

Identification of Drug Interactions Involving Antiretroviral

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ABSTRACT

Background: Increasingly, HIV management is complicated by chronic medical disorders and metabolic toxicities of treatment that require drugs, which may interact with ART. Identifying drug interactions among antiretrovirals (ARVs) and between ART and other drugs may prevent morbidity and treatment failure. We evaluated drug interactions involving ART in patients treated by HIV specialists in an urban population. **Methods:** Potential drug interactions were retrospectively identified from New York State Medicaid records of all oral, injectable and transdermal medications dispensed during a 6 month time period (10/05 to 3/06) to members of MetroPlus' Special Needs Plan for HIV (a Medicaid HMO) treated across 22 HIV clinics in NYC. Drug interactions were screened using Micromedex® and the University of Liverpool drug interactions program (www.hiv-druginteractions.org). Feedback was provided to all clinicians. **Results:** 11,935 non-unique medications were dispensed to 571 HIV+ patients. After excluding topical medications, 550 patients used an average of 6 medications each, of whom 342 (62%) were on at least one ARV. 129 potentially significant drug interactions were identified among 103 persons. 30% of patients on ART had at least one drug interaction involving their ARV agent. Interactions between ARV agents included: tenofovir (TDF) + atazanavir without ritonavir (RTV) (n = 11 of 129 [9%]), unadjusted PI dosed with NNRTI (n = 6 [5%]), and didanosine at 400 mg + TDF (n = 5 [4%]). The most common interactions between ARVs and other drugs were: psychotropic medications + RTV (n = 80 [62%]), anti-seizure medications + RTV/PI (n = 9 [7%]), and atazanavir + a proton pump inhibitor (n = 4 [3%]). Use of contraindicated statins was not found. 26 individuals had one or more drug interactions that could have caused reduced ARV levels (6 of 14 with available concurrent HIV plasma viral load (43% had a confirmed viral load of > 50 copies/ml during the period of the drug interaction). **Conclusions:** 1 in 3 ARV-treated patients managed by HIV specialists had a potentially significant ARV-related drug interaction, of whom over a quarter had an interaction that could compromise HIV suppression by causing suboptimal ARV levels. Managed care and Medicaid pharmacy dispensing databases can be valuable tools for early identification of potential drug interactions in an era of polypharmacy in the management of HIV infection.

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BACKGROUND

The use of combination antiretroviral therapy has decreased the morbidity and mortality associated with HIV infection. In addition to HIV drugs, patients living with HIV are often prescribed medications to treat co-morbid conditions such as diabetes, hyperlipidemia, depression and gastrointestinal disorders. HIV drugs can interact with each other, sometimes favorably. For example, ritonavir, a protease inhibitor, is a potent inhibitor of cytochrome P450 CYP3A4 and boosts the levels of protease inhibitors co-administered with this drug. However, efavirenz, a NNRTI, can substantially lower the levels of HIV-1 protease inhibitors, by inducing cytochrome P450 CYP3A4, which may compromise virologic response. HIV drugs can also interact with non-HIV drugs. For example, ritonavir inhibits the metabolism of certain "statins", which can lead to hepatic toxicity and/or rhabdomyolysis. Moreover, HIV primary care providers (PCPs) may not be aware of these interactions or may not have the information that other providers or specialists had prescribed interacting medications.

Objective: To determine the prevalence and describe the types of drug interactions involving antiretroviral agents among HIV-infected patients.

Methods:

- MetroPlus Health Plan is a Health Maintenance Organization (HMO) that provides care to persons with Medicaid residing within 4 New York City Boroughs (Manhattan, the Bronx, Brooklyn or Queens). The Partnership in Care (PIC) Program is MetroPlus' Special Needs Plan (SNP) for persons with HIV infection. Enrollment in PIC is voluntary and provides enhanced case management and ensures access to an HIV specialist PCP.
- Retrospective review of the pharmacy database provided by New York State Medicaid to screen all SNP members prescribed antiretroviral drugs within 180 days prior to March 31, 2006 for key potential adverse drug interactions (Table 1).
- Any SNP member continuously enrolled for ≥ 3 months prior to the baseline review of potential drug interactions.
- Pharmacy database review: Prescriptions dispensed within 6 months prior to March 2006 to identify those members prescribed medications that have interactions. Medical providers were informed in July 2006 of the potential drug interactions involving their individual patients identified by the review. An overall summary of identified interactions was also provided for educational purposes.
- A second review was conducted in November 2006 to identify drug interactions involving ART during August to October 2006 to assess the impact of feedback provided in July 2006.
- HIV-1 plasma viral load were obtained for the period prior to and after initiation of antiretroviral regimens in which a drug interaction was identified that might potentially lower the drug exposure to at least one ARV.
- Drug interactions were screened using Micromedex® and the University of Liverpool drug interactions program (www.hiv-druginteractions.org).

Therapy (ART) in New York City HIV Specialty Clinics

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Table 1: Examples of Screened Drug Interactions

Drug 1	Drug 2	Interaction
Atazanavir	PPIs/H2 Blockers	Lowered atazanavir levels
Tenofovir	Didanosine	Increased didanosine levels
Tenofovir	Atazanavir	Lowered atazanavir levels
Simvastatin	Protease Inhibitors	Increased statin levels
Phenytoin Phenobarbitol Carbamazepine	Protease Inhibitors	Lowered protease inhibitor levels
Voriconazole	Efavirenz Ritonavir (> 400 mg BID)	Lowered voriconazole levels
Rifampin	Protease Inhibitors	Lowered protease inhibitor levels
Psychotropic Medications	Protease inhibitors	Increased psychotropic medication levels

Table 2: Most Common Drug Interactions Involving ARV by review period

Drug 1	Drug 2	Initial Review n (%) Total Drug-Drug interactions: 129	Follow-up Review n (%) Total Drug-Drug interactions: 148
Atazanavir	PPIs/H2 Blockers	4 (3)	9 (6)
Tenofovir	Didanosine ^Δ	5 (4)	6 (4)
Tenofovir	Atazanavir ^Δ	11 (9)	9 (6)
Protease Inhibitor ^Δ	NNRTI	6 (5)	6 (4)
Phenytoin Phenobarbitol Carbamazepine	Protease Inhibitors	9 (7)	9 (6)
Psychotropic Medications*	Protease inhibitors	80 (62)	101 (68)

^Δ Dose not adjusted

* Most Common: benzodiazepines, haloperidol, mirtazapine, paroxetine, sertraline, venlafaxine, zolpidem.

** Other ARV-ARV Interactions identified: epzicom® + atazanavir (300 mg); r/atazanavir (100/400 mg); r/tipranavir (100/500 mg BID); fosAmprenavir+lopinavir/r; stavudine+zidovudine

RESULTS

Initial Review (October 2005-March 2006):

- 11,935 non-unique medications were dispensed to 571 HIV+ patients.
- After excluding topical medications, 550 patients used an average of 6 medications each, of whom 342 (62%) were on at least one ARV.
- 129 potentially significant drug interactions were identified among 103 persons (Table 2).
- 30% of patients on ART had at least one drug interaction involving their ARV agent.
- 26 individuals had one or more drug interactions that could have caused reduced ARV levels (6 of 14 with available concurrent HIV plasma viral load [43%] had a confirmed viral load of > 50 copies/ml during the period of the drug interaction).

FOLLOW-UP REVIEW (August 2006-October 2006):

- After excluding topical medications, 689 patients were on at least one ARV.
- 148 potentially significant drug interactions were identified among 103 persons (Table 2).
- 15% of patients on ART had at least one drug interaction involving their ARV agent.
- 28 individuals had one or more drug interactions that could have caused reduced ARV levels (9 of 19 with available concurrent HIV plasma viral load [47%] had a confirmed viral load of > 50 copies/ml during the period of the drug interaction).

Follow-up:

- 39 patients with 49 drug interactions involving ARV agents either between 2 ARVs (n = 15 interactions) or between ARVs and other drugs (n = 34 interactions) were included in both reviews (March and October 2006). All patients' HIV PCPs had received a memo indicating the potential drug interaction identified.
- Overall 19 (39%) had corrected the noted interaction.
- Among 12 ARV-ARV interactions that could have caused a decrease in ARV exposure to one of the agents, 4 (33%) had corrected the interaction. 2 of 3 with unsuppressed viral load had corrected the interaction.

CONCLUSIONS:

- Overall 1 in 5 patients receiving ART had a potential drug interaction.
- 20% of these interactions could have caused reduced ARV levels which may compromise virologic suppression.
- Managed care and Medicaid pharmacy dispensing record review can be a powerful tool to identify potential drug interactions promptly and may prevent drug resistance from developing, especially if multiple providers may be prescribing therapy.