Antiretroviral Drug Exposures Reported to Texas Poison Centers

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Abstract

Background. A number of different antiretroviral drugs are used to manage patients with human immunodeficiency virus (HIV). **Objective.** This study describes antiretroviral drug exposures reported to a large statewide poison center system. **Methods.** Cases were all antiretroviral drug exposures reported to the Texas Poison Center Network during 2000 to 2014. The distribution of cases was determined for various demographic and clinical factors. **Results.** Of a total of 632 exposures, the most commonly reported drugs were emtricitabine–tenofovir combination (17.1%), efavirenz–emtricitabine–tenofovir combination (13.8%), ritonavir (10.9%), lamivudine–zidovudine combination (10.3%), and efavirenz (10.1%). The annual number of antiretroviral drug exposures increased from 34 in 2000 to 67 in 2014. Males comprised 67.9% of the patients; 72.2% were 20 years or older. The exposures were 58.5% unintentional and 37.5% intentional. Only antiretroviral drugs were reported in 440 of the exposures. Of these exposures, 62.5% were managed on site, 28.0% were already at or en route to a health care facility when the poison center was contacted, and 8.6% were referred to a health care facility. The exposures were not serious in 88.7% of these cases. The most frequently reported adverse clinical effects were vomiting (5.7%), nausea (4.8%), dizziness/vertigo (3.2%), and drowsiness/lethargy (3.2%). **Conclusions.** The most commonly reported antiretroviral drugs were emtricitabine–tenofovir combination and efavirenz–emtricitabine–tenofovir combination. The patients were most likely to be adults and males. The exposures tended to be unintentional. Of those exposures involving only antiretroviral drugs, the majority of the exposures were not serious and could be managed outside of a health care facility.

Keywords

antiretroviral drug, poison center, management, outcome

Introduction

According to the Centers for Disease Control and Prevention, as of 2011 over 1.2 million persons 13 years or older in the United States were living with human immunodeficiency virus (HIV) infection. From 2007 to 2011, the number of persons living with HIV increased 7.2%. Approximately 50 000 new infections occur each year.¹ According to the Texas Department of State Health Services, as of 2013 over 76 000 persons in Texas were known to have HIV. There were more than 3 times the number of male as female persons known to have HIV. Almost half of the persons were 45 years or older. While blacks represented approximately 11% of the Texas population in 2013, they accounted for the largest proportion of persons known to have HIV.²

The drugs used for the management of patients with HIV and acquired immunodeficiency syndrome are called antiretrovirals because they operate against the HIV retrovirus. These drugs are grouped into major classes based on the manner in which they interfere in the HIV replication.³

Entry inhibitors hinder the binding of the HIV virus to receptors on the outer surface of the cell it attempts to enter. Fusion inhibitors interfere with the ability of the virus to fuse with the cellular membrane. Reverse transcriptase inhibitors obstruct the HIV enzyme reverse transcriptase from converting HIV RNA into HIV DNA. There are 2 types of reverse transcriptase inhibitors: nucleoside reverse transcriptase inhibitors (NRTIs) are defective DNA building blocks. When one of these building blocks is added to a growing HIV DNA chain, it prevents correct DNA building blocks from being added on and halts HIV DNA synthesis. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) attach to reverse transcriptase, hindering its ability to convert HIV RNA into HIV DNA. Integrase inhibitors

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obstruct HIV integrase, the enzyme the virus uses to integrate its genetic material into the infected cell's DNA. Protease inhibitors (PIs) interfere with the enzyme protease, which is needed to cut long chains of HIV proteins into smaller proteins, thus preventing new virus particles from being assembled. Multiclass combination products combine HIV drugs from 2 or more of these classes into a single product. To prevent the emergence of HIV strains resistant to a particular antiretroviral drug, it is recommended that persons with HIV take a combination of antiretroviral drugs, a procedure called highly active antiretroviral therapy.³

Not only are antiretroviral drugs recommended for patients with HIV, but in recent years it has been suggested that people who do not have HIV but are at high risk of becoming infected prevent infection by taking antiretroviral drugs daily, an approach called preexposure prophylaxis (PrEP). The drug recommended in PrEP is a combination of 2 antiretrovirals, tenofovir and emtricitabine.^{4,5} Implementation of PrEP might lead to an increased number of individuals exposed to antiretrovirals.

Adverse clinical effects have been reported with all antiretroviral drugs and are a frequent reason for patients changing or discontinuing drug treatment. Since many of the antiretroviral drugs are used in combination, there is the risk of overlapping and additive toxicities. However, the rate of adverse effects appears to be lower with newer drugs and drug regimens.⁶ Some of the more commonly reported chronic and acute adverse effects include lactic acidosis, lipodystrophy, hyperlipidemia, rash, liver toxicity, peripheral neuropathy, headache, diarrhea, nausea, and vomiting.^{6,7}

Poison centers are telephone consultation services that assist in the management of potentially adverse exposures to a variety of substances. In 2013, 675 antiretroviral drug exposures were reported to US poison centers.⁸ During 2001 to 2013, at least 6 deaths involving antiretroviral drugs were reported to these poison centers.⁹⁻¹²

Few studies have examined antiretroviral drug exposures reported to poison centers.¹³⁻¹⁵ The intent of this investigation was to describe antiretroviral drug exposures reported to a large statewide poison center system.

Materials and Methods

This retrospective epidemiologic study used data collected by the Texas Poison Center Network (TPCN), which consists of 6 poison centers that together service the entire state, a population of over 25 million. The 6 poison centers use a common electronic database to collect information on all calls in a consistent manner. The data variables and allowable codes in this database were standardized by the American Association of Poison Control Centers.¹⁶

Cases were all exposures to antiretroviral drugs reported to the TPCN during 2000 to 2014. Exposures involving other substances in addition to the antiretroviral drug and exposures

not followed to a final medical outcome were included. The distribution of cases was determined for the following variables: specific antiretroviral drug and drug class, number of antiretroviral drugs, year, patient age and gender, exposure route, circumstances of (reason for) exposure, exposure site, management site, medical outcome, and most commonly reported adverse clinical effects and treatments. The analysis of management and outcome was performed for those exposures involving only antiretroviral drugs because the other substance might have affected the management and outcome.

For the number of antiretroviral drugs in an exposure, combination drugs such as emtricitabine–tenofovir combination were classified as a single drug. For exposure reason, the major categories were unintentional (ie, accidental, therapeutic error), intentional (ie, suspected attempted suicide, intentional misuse or abuse), adverse reaction to the product, other, and unknown. The medical outcome or severity of an exposure is assigned by the poison center staff and is based on the observed or anticipated adverse clinical effects. Medical outcome is classified according to the following criteria: no effect (no symptoms due to exposure), minor effect (some minimally troublesome symptoms), moderate effect (more pronounced, prolonged symptoms), major effect (symptoms that are life-threatening or cause significant disability or disfigurement), and death. A portion of exposures are not followed to a final medical outcome because of resource constraints or the inability to obtain subsequent information on the patient. In these instances, the poison center staff record the expected outcome of the exposure. These expected outcomes are grouped into the following categories: not followed but judged as nontoxic exposure (symptoms not expected), not followed but minimal symptoms possible (no more than minor symptoms possible), unable to follow but judged as a potentially toxic exposure. Another medical outcome category is unrelated effect where the exposure was probably not responsible for the symptoms. The analysis of medical outcome was performed for these specific outcomes as well as grouping the outcomes into those known or expected to not be serious (no effect, minor effect, not followed and judged nontoxic, not followed and judged minimal effects) and those known or expected to be serious (moderate effect, major effect, death, unable to follow and potentially toxic).

The Texas Department of State Health Services institutional review board considers this investigation exempt from ethical review.

Results

A total of 632 exposures met the study criteria. Table 1 shows the distribution of the exposures by drug class and specific drug. The most commonly reported drug classes were NRTIs followed by PIs and multiclass combination products. The most commonly reported specific drugs were

Table 1. Antiretroviral Drug Exposures Reported to the Texas Poison Center Network During 2000 to 2014 by Type of Drug^a.

Drug	Number	% Total
Nucleoside reverse transcriptase inhibitors (NRTIs)	345	54.6
Emtricitabine and tenofovir	108	17.1
Lamivudine and zidovudine	65	10.3
Lamivudine	54	8.5
Stavudine	36	5.7
Tenofovir	30	4.7
Zidovudine	27	4.3
Abacavir, lamivudine, zidovudine	21	3.3
Abacavir and lamivudine	17	2.7
Abacavir	16	2.5
Didanosine	15	2.4
Emtricitabine	5	0.8
Carbovir	1	0.2
Protease inhibitors (PIs)	196	31.0
Ritonavir	69	10.9
Atazanavir	35	5.5
Lopinavir	35	5.5
Nelfinavir	34	5.4
Darunavir	28	4.4
Saquinavir	11	1.7
Fosamprenavir	8	1.3
Indinavir	8	1.3
Amprenavir	6	0.9
Lopinavir and ritonavir	5	0.8
Multiclass combination products	108	17.1
Efavirenz, emtricitabine, tenofovir	87	13.8
Emtricitabine, rilpivirine, tenofovir	12	1.9
Cobicistat, elvitegravir, emtricitabine, tenofovir	9	1.4
Nonnucleoside reverse transcriptase inhibitors (NNRTIs)	102	16.1
Efavirenz	64	10.1
Nevirapine	33	5.2
Etravirine	5	0.8
Delavirdine	1	0.2
HIV integrase strand transfer inhibitors	22	3.5
Raltegravir	13	2.1
Dolutegravir	6	0.9
HIV-I integrase inhibitor, unspecified	3	0.5
Entry inhibitors (CCR5 coreceptor antagonist)	2	0.3
Maraviroc	2	0.3
Fusion inhibitors	1	0.2
Antiretroviral drug, unknown	5	0.8
Total	632	

^aA given exposure might involve more than one antiretroviral drug.

emtricitabine–tenofovir combination, efavirenz–emtricitabine–tenofovir combination, ritonavir, lamivudine–zidovudine combination, and efavirenz. One antiretroviral drug (a single drug or multiple drugs that occur as a combination) was reported in 461 (72.9%) exposures, 2 drugs in 104 (16.5%) exposures, 3 drugs in 62 (9.8%) exposures, and 4 drugs in 5 (0.8%) exposures.

The annual number of antiretroviral drug exposures increased from 34 in 2000 to 67 in 2014. Males comprised 429 (67.9%) of the patients, females 200 (31.6%), and unknown gender 3 (0.5%). The age distribution of the patients was 132 (20.9%) 5 years or less, 6 (0.9%) 6 to 12 years, 32 (5.1%) 13 to 19 years, 456 (72.2%) 20 years or older, and 6 (0.9%) unknown age.

Table 2. Antiretroviral Drug Exposures Reported to the Texas Poison Center Network During 2000 to 2014 by Exposure Reason.

Exposure Reason	Number	% Total
Unintentional	370	58.5
General	138	21.8
Occupational	4	0.6
Therapeutic error	225	35.6
Misuse	3	0.5
Intentional	237	37.5
Suspected attempted suicide	213	33.7
Misuse	14	2.2
Abuse	2	0.3
Unknown	8	1.3
Adverse drug reaction	20	3.2
Other—malicious	1	0.2
Unknown	4	0.6
Total	632	

The route of the exposure was 624 (98.7%) ingestion, 5 (0.8%) ocular, 4 (0.6%) parenteral, 3 (0.5%) inhalation, 2 (0.3%) dermal, and 2 (0.3%) unspecified other. (An exposure might involve more than one route.) The majority of the exposures were unintentional (Table 2). The exposure site was 578 (91.5%) patient's own residence, 8 (1.3%) another residence, 5 (0.8%) workplace, 8 (1.3%) health care facility, 2 (0.3%) school, 10 (1.6%) public area, 15 (2.4%) unspecified other, and 6 (0.9%) unknown.

Only antiretroviral drugs were reported in 440 (69.6%) exposures and other substances in addition to the antiretroviral drugs in 192 (30.4%) of the exposures. Of the 440 exposures with only antiretroviral drugs, 275 (62.5%) of the patients were managed on site (outside of a health care facility), 123 (28.0%) were already at or en route to a health care facility when the poison center was contacted, 38 (8.6%) were referred to a health care facility by the poison center, 2 (0.5%) were managed at an unspecified other location, and 2 (0.5%) were managed at an unknown location.

Table 3 shows the distribution of antiretroviral drug exposures by medical outcome. The majority of the exposures were known or expected to not be serious. The most frequently reported adverse clinical effects were vomiting ($n = 25$, 5.7%), nausea ($n = 21$, 4.8%), dizziness/vertigo ($n = 14$, 3.2%), and drowsiness/lethargy ($n = 14$, 3.2%). The most commonly reported treatments were dilution ($n = 108$, 24.5%), food/snack ($n = 55$, 12.5%), activated charcoal ($n = 49$, 11.1%), intravenous fluids ($n = 32$, 7.3%), cathartic ($n = 30$, 6.8%), and lavage ($n = 11$, 2.5%).

Of the 49 exposures involving only antiretroviral drugs where the medical outcome was serious, 39 (79.6%) involved patients age 20 years or more, 35 (71.4%) patients were male, and 29 (59.2%) were suspected attempted suicides. The one death was an adult male who had ingested

Table 3. Antiretroviral Drug Exposures Reported to the Texas Poison Center Network During 2000 to 2014 by Medical Outcome^a.

Medical Outcome	Number	% Total
No effect*	117	26.6
Minor effect*	34	7.7
Moderate effect**	16	3.6
Major effect**	0	0.0
Death**	1	0.2
Not followed—judged as nontoxic*	40	9.1
Not followed—minimal clinical effects expected*	192	43.6
Unable to follow—judged potentially toxic**	32	7.3
Unrelated effect	8	1.8
*Not serious	383	87.0
**Serious	49	11.1
Total	440	

^aIncludes only exposures to antiretroviral drugs and not also other substances.

emtricitabine and tenofovir combination and experienced hypotension, lactic acidosis, and hypoglycemia. Details as to the cause of death were not provided.

Discussion

Over half of the antiretroviral drug exposures reported to Texas poison centers involved NRTIs and over 30% involved PIs. The most commonly reported specific antiretroviral drugs were emtricitabine–tenofovir combination (an NRTI), reported in over one sixth of all exposures, followed by efavirenz–emtricitabine–tenofovir combination (a multi-class combination drug), ritonavir (a PI), lamivudine–zidovudine combination (an NRTI), and efavirenz (an NNRTI). This pattern differs from the previous poison center studies. In the study using California poison center data for 1998 to 2005, the most common antiretroviral drugs were lamivudine (36%), zidovudine (24%), stavudine (20%), and efavirenz (15%).¹⁵ In the investigation based on Georgia poison center data for 2001 to 2010, zidovudine was the most common antiretroviral drug, reported in 28% of the exposures.¹⁴ The differences between the studies may be due to differences in time periods included, classification of the antiretroviral drugs, or inclusion criteria. For instance, the emtricitabine–tenofovir combination was approved by the US Food and Drug Administration in 2004, so the California poison center study, and to a lesser extent the Georgia poison center study, would not be likely include many exposures to this drug. Prescription and sales data for specific antiretroviral drugs are not available in Texas, so a comparison with the exposures to specific antiretroviral drugs and drug classes reported to Texas poison centers was not possible.

Over one quarter of the exposures involved more than one antiretroviral drug. This is not surprising considering that it is recommended that persons with HIV take a combination of antiretroviral drugs.³ This suggests that when health care providers are managing a potentially adverse exposure to an antiretroviral drug, they may want to identify all of the antiretroviral drugs involved in the exposure. The potential use of multiple antiretroviral drugs, as well as the fact that a number of the antiretroviral drugs consist of multiple drugs in combination, may need to be taken into consideration when trying to determine the appropriate management and likely outcome of potentially adverse exposures to these drugs.

The annual number of antiretroviral drug exposures almost doubled between 2000 and 2014. The number of persons living with HIV in the United States is increasing.¹ Moreover, in recent years PrEP has been suggested for people who do not have HIV but are at high risk of becoming infected.^{4,5} These 2 factors might be expected to lead to an increase in antiretroviral drug use, and consequently an increase in the number of antiretroviral drug exposures reported to poison centers. In contrast, the Georgia study identified no annual trend in antiretroviral drug exposures.¹⁴

Over two thirds of the patients were males and over 70% were adults. This is consistent with the general pattern of HIV in Texas. As of 2013, in Texas there were more than 3 times the number of male as female persons known to have HIV, and adults accounted for the majority of persons known to have HIV.² In the California study, 72% of the patients were male and the median age was 31 years, with 33% being children.¹⁵ In the Georgia study, 62% of the patients were male and the mean age was 27 years.¹⁴

Almost 60% of the exposures were unintentional and 40% intentional. The most commonly reported specific circumstances of the exposure were therapeutic error (36%) and suspected attempted suicide (34%). This pattern was similar to that reported in the previous investigations. In the California study, 51% of the exposures were unintentional or medication errors, 38% intentional, and 9% adverse reactions.¹⁵ In the Georgia study, 30% of the exposures were intentional and 70% unintentional, adverse reaction, or unknown reason. Of the intentional exposures, 96% were suspected attempted suicide; of the unintentional exposures, 58% were therapeutic errors.¹⁴

Almost 90% of the exposures were known or expected to not have serious outcomes. As a consequence, it might be expected that the majority of the patients would not need to be managed at a health care facility. In fact, 63% of the patients were managed outside of a health care facility. If the exposures are limited only to those 313 patients over which the poison center might exert some control over where the patient is managed (ie, on site or referred to a health care facility), 88% were managed on site and 12% were referred to a health care facility.

The most commonly reported adverse clinical effects were vomiting, nausea, dizziness/vertigo, and drowsiness/lethargy. These clinical effects are consistent with those reported in the literature.^{6,7} The most frequently reported treatments tended to be administration of some form of decontamination - dilution, food/snack, activated charcoal, cathartic, and lavage.

This investigation is subject to various limitations. Texas poison centers were used as a data source. In spite of Texas having a current population of over 25 million, only 632 cases were identified over a 15-year period. It is unlikely that all potentially adverse antiretroviral drug exposures are reported to poison centers. Thus, the exposures reported to poison centers are not likely to indicate the actual number of potentially adverse exposures to these drugs. In addition, those exposures that are reported to poison centers may not be representative of all such exposures that occur. Health care facilities or infectious disease specialists might serve as alternative data sources. However, in this study, the majority of potentially adverse antiretroviral drug exposures were not seen by health care providers. Such exposures might be missed in studies using health care facilities or infectious disease specialists as data sources. An advantage of using poison centers as a data source is that they would include cases that might be missed by these other data sources.

Exposure to a retroviral drug was generally based on a report by the patient or the person contacting a poison center and not verified clinically. As a result, some cases might not actually have been actual antiretroviral drug exposures.

Moreover, this study examined antiretroviral drugs as a group. Many of the antiretroviral drugs are used in combination; therefore, there is the possibility of overlapping and additive toxicities. Examination of individual antiretroviral drugs would be difficult because relatively few of the exposures would likely involve only that drug. For example, of the 108 exposures to the emtricitabine-tenofovir combination, only 39% involved only that drug. So while this study may be of limited utility for evaluating the management and outcome of antiretroviral drug exposures, it does provide information on the demographics and circumstances of such exposures.

The majority of patients were not managed at a health care facility and a number were not followed to a final medical outcome. So conclusions on the effects of the exposures and outcomes in many cases did not involve clinical evaluation by a health care provider.

Information on the patients prescribed antiretroviral drugs in Texas, such as the type of drug prescribed, and the patient's demographics, is not readily available, so the patterns observed in poison center exposures cannot be compared to prescription patterns.

In conclusion, potentially adverse antiretroviral drug exposures reported to Texas poison centers increased over

the recent 15-year period. The most common antiretroviral were NRTIs and PIs. The patients were most likely to be adults and males. The exposures tended to be due to therapeutic errors or suspected attempted suicide and occurred by ingestion. Of those exposures involving only antiretroviral drugs, the majority were not serious and could be managed outside of a health care facility. Pharmacists and health care providers who interact with individuals prescribed antiretroviral drugs may consider educating the individuals as to the proper way to take and store the drugs to reduce potentially adverse exposures.

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