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Dermatological conditions associated with HIV medication in a cohort of Greek patients initiating antiretroviral therapy: 1988–2013

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Abstract

Objectives: Treatment of HIV infection has evolved from a single antiretroviral agent to combination therapy, which has dramatically improved both the quality of life and life expectancy of affected patients. The aim of this study was to review HIV treatment-associated dermatological conditions observed in adult patients receiving antiretroviral therapy (ART) in a single tertiary care referral centre over time.

Methods: We reviewed the files of HIV-positive patients seen at the Dermatology Department, AIDS Clinic of the Andreas Syggros Hospital, Athens, Greece who had initiated ART from 1988 to 2013, for evidence of dermatological conditions commonly associated with HIV-related medication.

Results: Among a cohort of 1329 HIV-positive patients (1155 men and 174 women), 352 (299 men and 53 women) presented with at least one dermatological condition, with a total of 423 conditions diagnosed that could be attributed to HIV-related medication. Lipodystrophy (47.42%), and maculopapular (MP) rash (40.6%) were most commonly diagnosed. There were three incidence peaks for these reactions, which reflected the different types of ART and HIV-related drugs commonly used at the time. After 2006, the number of these dermatological conditions declined (15.1% of cases) with the availability of newer ART regimens.

Conclusions: Early ART was accompanied with a high incidence of adverse skin reactions, which have decreased over time in association with overall better tolerated treatment regimens for HIV infection

Keywords: ART, HIV medication, dermatological reactions, lipodystrophy, maculopapular rash

Introduction

Reporting of HIV cases in Greece started in the early 1980s. The epidemic among the Greek population was initially of subtype B, with a recent increase in non-B subtypes, especially subtype A [1–3]. Treatment over time has evolved from monotherapy to combination antiretroviral therapy (ART). Zidovudine (AZT) was introduced in 1987 and used as monotherapy with limited impact on the course of the disease [4,5]. *Pneumocystis jirovecii* pneumonia was a very common opportunistic infection at that time and was prevented and/or treated with trimethoprim-sulfamethoxazole (TMP-SMX). Both these agents are known to cause adverse cutaneous reactions [6–8]. Combination ART was introduced in 1996 as a triple-drug regimen that included two new drug classes, non-nucleoside inhibitors of HIV retrotranscriptase (NNRTIs) and protease inhibitors (PIs) and was associated with a dramatic decrease in morbidity and mortality, but also with drug reactions, especially during the early years of their introduction into clinical practice [4,5]. The more recent ART regimens, which include integrase inhibitors, next generation NNRTIs and PIs, as well as entry inhibitors have displayed a similar or increased effectiveness and, generally, an overall safer profile [4,9]. Our aim in this study was to review the number and type of dermatological conditions considered to be related to HIV treatment in patients on ART in a 25-year period in a large outpatient unit in Athens, Greece.

Methods

This is a retrospective review of dermatological conditions in ART-treated HIV patients at the outpatient Dermatology Department, AIDS Unit of the Andreas Syggros Hospital, a tertiary care referral centre in Athens, Greece during the period 1988–2013. This outpatient department specialises in diagnosing, monitoring and treating HIV patients. The individuals included in this study were ART naive or already under antiretroviral therapy.

We reviewed patients' files for evidence of dermatological conditions considered commonly associated with ART, drugs used for prophylaxis, treatment of HIV-1 related conditions, and opportunistic infections (OIs). We included clinically diagnosed lipodystrophy in the dermatological conditions described. Lipodystrophy was considered if lipoatrophy or central, submandibular, dorso-cervical and/or breast fat accumulation were present. The review was carried out under careful protection of patients' confidentiality. Written consent or ethics approval were not sought because the given treatment was based on national guidelines and was not part of primary research or protocol. All the data were collected from charts and anonymised. The retrospective analysis on blood-test results that were ordered during routine follow-up consultations for diagnosis and treatment was made part of the audit to review the effectiveness of treatment and quality of care given to the HIV-infected patients of our HIV unit.

We collected patient baseline characteristics (Tables 1 and 2). The most probable causative agent was assigned according to its known association with the dermatological condition diagnosed. In the case of multiple dermatological conditions in a single patient, each event was recorded separately. The commonest dermatological conditions seen in a single patient were lipodystrophy and maculopapular rash. It was uncommon for two cases of maculopapular (MP) rash to affect a person at the same time, but co-existence of maculopapular rash and lipodystrophy could occur. Cases of more than one maculopapular rash in the same patient occurred over time. Rash disappearance after drug withdrawal or its reappearance after challenge confirmed causality.

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Table 1. Population characteristics of individuals with HIV treatment-related dermatological reactions

Characteristic	Number of patients with reactions (total number=352) *n* (%)	Number of reactions (total number=423) *n* (%)
Sex		
Male	299 (84.9)	352 (83.2)
Female	53 (15.1)	71 (16.8)
Age group,(years)		
<30	112 (32)	126 (29.8)
31–40	132 (37.7)	168 (39.8)
41–50	7 (20.3)	86 (20.5)
>50	35 (10)	43 (9.9)
Ethnicity		
Greek	326 (92.6)	391 (92.3)
Balkan	6 (1.7)	6 (1.4)
European (other than Balkan)	6 (1.7)	7 (1.7)
African	10 (2.86)	14 (3.4)
Asian/other	4 (1.14)	5 (1.2)
CD4 cell count at time of reaction (cells/mm^3)		
<200	–	116 (27.4)
201–350	–	86 (20.4)
351–500	–	77 (18.2)
>501	–	144 (34)

Table 2. Antiretroviral medication given at time of skin reactions related to HAART

Combination and number of HAART treatments	Number of individuals (total number=176) *n*
NNRTI+2NRTI	32
2NRTI+PI	91
3NRTI	5
2NRTI+2PI	22
NNRTI+NRTI+PI	3
2NRTI	19
2PI	2
2NRTI+PI+II	1
NNRTI+NRTI+PI+II	1

HAART: highly active antiretroviral treatment; II: integrase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; PI: protease inhibitor.

We have estimated the incidence of HIV drug-associated dermatological reactions during the period 1988–2013 for our patient population and looked at its distribution over time. Data were analysed using Stata version 13. Chi-squared tests were used to determine whether there was a significant association between the two categorical variables, and a *P*-value<0.05 was considered statistically significant.

Results

In this retrospective study of 1329 adult patients from a Greek tertiary referral outpatient department who were taking ART, 738 did not receive treatment for more than 1 month or have a second follow-up visit. The mean ART duration of the 1329 patients was 4–5 years.

The mean age of patients who presented with reactions was 36.9 years, 352 patients (299 men and 53 women) presented with at least one dermatological condition considered to be associated with HIV medication. In total, there were 423 dermatological conditions associated with HIV treatment, 352 of them in men and 71 in women (Table 1).

Forty-five patients presented with multiple dermatological conditions (37 patients had two conditions, six had three, one had four, and one had five). As mentioned earlier, the commonest reactions appearing in a single patient were maculopapular rash and lipodystrophy.

Whenever a drug was considered responsible for the event, it was subsequently discontinued when the reaction was severe or life threatening. Switch of antiretroviral medication was also indicated in benign cases such as lipodystrophy when cosmetic disfigurement had a large impact on a patient's quality of life.

There was no difference between the sexes in terms of the number of conditions (χ^2=1.62, *P*=0.20). The majority of dermatological reactions related to HIV medication observed over this 25-year period in ART-treated patients included lipodystrophy (47.42% of all cases) and MP eruptions (40.6%). Other important HIV drug-related conditions were acute urticaria (5.64%), Stevens–Johnson syndrome (0.24%), erythema multiforme (0.7%), and Lyell's syndrome (1.2%). Photosensitivity, nail pigmentation and generalised pigmentation (other conditions) accounted for 4.3% of all cases (Table 3). The distribution of dermatological conditions attributed to HIV-related medication over time was examined (Figure 1, Table 4).

Based on their distribution over time (Figure 1), we divided the dermatological conditions into three consecutive periods that coincided with different types of ART. There was an almost five-fold increase in conditions during the second period (introduction of combination ART and use of stavudine) with around one in three patients (30.5%) presenting with a dermatological condition considered secondary to ART or to another drug such as TMP-SMX.

There were 201 documented cases of lipodystrophy in a total of 180 patients (172 in men and 29 in women) with the majority (152 cases) reported during the second ART period (1997–2006). During the first ART period (1988–1996), there were 13 cases and during the last period (2007–2013), 36 cases. The majority were attributed to the use of indinavir (IDV) (93 cases, 46.3%) followed by stavudine (d4T) (32 cases, 16%), lopinavir/ritonavir (18 cases, 9%), and ritonavir (RTV) (16 cases, 8%). In total, there were 172 MP eruptions, 141 in men and 31 in women, associated with the following agents: TMP-SMX (27.6%), nevirapine (NVP) (25.6%), ART other than NVP (16%), beta-lactam antibiotics (12%), other types of antibiotics, anti-malaria drugs like atovaquone, and pentamidine used against *Leishmania* infection (11%). The remaining cases were attributed to antifungal agents (3%) and other medication (4.78%). The majority of MP eruptions (100 cases) were observed during the second ART period (with 26 and 46 documented cases in the first and last ART periods, respectively. Maculopapular eruptions associated with TMP-SMX were mostly observed during the first ART period. Those related to NVP (44 cases) occurred mostly during the second ART period with a higher incidence in women (13 cases, 15%) than in men (31 cases, 7.5%) (*P*=0.03, risk ratio [RR]=2077, 95% confidence interval [CI] 1135–3799).

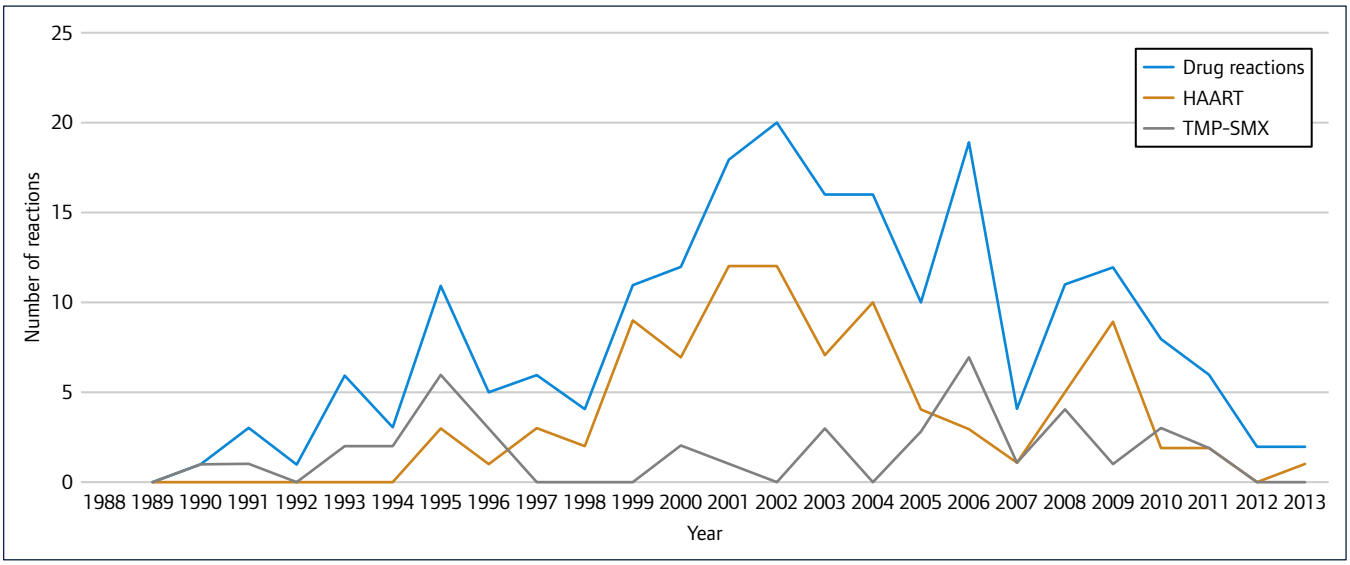

Figure 1. Number of HIV treatment-related dermatological conditions in patients initiated on antiretroviral therapy 1988–2013.

Table 3. Dermatological conditions in 423 individuals initiated on ART

Dermatological condition	Males (total number=352) *n*	Females (total number=71) *n*	Total *n* (%)
Lipodystrophy	172	29	201 (47.42)
Maculopapular rash	141	31	172 (40.6)
Acute urticaria	16	7	23 (5.64)
Lyell's syndrome	5	0	5 (1.2)
Stevens–Johnson syndrome	1	0	1 (0.24)
Erythema multiforme	3	0	3 (0.7)
Others	14	4	18 (4.3%)

Table 4. Dermatological reactions over time according to type of ART

Period	Dermatological reactions *n* (%)	Reactions per individual seen in that period % (number of reactions/number of individuals)
1988–1996	57 (13.7)	8.3 (57/686)
1997–2006	302 (71.6)	30.5 (302/990)
2007–2013	64 (15.1)	9.9 (64/646)
Total	**423**	–

Urticaria was documented in 23 cases and the drugs involved were: ART (33.3%); beta-lactam antibiotics (25%); and TMP-SMX (8.7%).

Severe forms of drug reaction occurred such as Stevens–Johnson (one case), Lyell's syndrome (five cases in men) and EM (three cases). The causative agent for Stevens–Johnson was abacavir, NVP (two cases), TMP-SMX (one case) and pyrimethamine use (two cases) resulted in Lyell's syndrome, and NNRTIs were implicated in EM cases. Zidovudine was associated with nail pigmentation in three cases and considered responsible for one of six cases of skin hyperpigmentation.

Discussion

In this retrospective study performed in a tertiary medical centre of Athens, Greece, we have shown that the incidence of drug reactions in our patient population who had initiated ART was highest during the period of introduction of triple therapy in the years 1997–2006 and has subsequently declined over time with the availability of the more recent treatment regimens. Lipodystrophy and MP rashes represented the majority of drug-related dermatological conditions. Our results are in line with evidence showing a better tolerability of the novel antiretroviral agents introduced since 2007 with a similar or enhanced virological efficacy [10,11]. Patients on ART have been described in several studies as showing a higher incidence of adverse drug reactions when compared to HIV-negative individuals. These reactions are estimated to be 100 times more common, and generally occur during the first year of treatment. The reason behind this increased incidence is believed to be multifactorial [6,12].

In our study HIV treatment-related dermatological conditions were observed in 352/1329 or 26.73% of ART-treated patients, which is substantially higher than in the general population where it is estimated to be 0–8% [13,14]. The number of affected men was 299 out of a total of 1154 (25.9%) who were on ART and 53 women of 174 women (30.4%), with no difference noted between sexes (χ^2=1.62, P=0.20) although the total number of affected women was small.

We have divided the distribution of drug reactions into three time periods, which coincided with changes in the main type of ART prescribed. The first peak period is observed in the period 1988–1996, the second in 1997–2006 and the third in 2007–2013 (Figure 1). Table 4 reflects the change of drug-reaction incidence per period. The first period was characterised by MP eruptions, attributed mostly to the administration of TMP-SMX, whereas NVP was the major causative agent for those observed during the second peak period.

Lipodystrophy and MP drug reactions attributed to NVP and other ART medications were mostly observed during the second ART period. TMP-SMX still accounted for some MPs, but the majority of them were then linked to NVP use that started in 1998.

According to some studies, the incidence of NVP-related reactions seemed to be double in women compared to men [15]. In our study there were 44 cases, of which 13 were in women and 31 in men. When corrected for the total number of men and women receiving NVP, the incidence was 15% in women and 7.5% in men (P=0.03, RR=2077, CI 95% 1135–3799), which is in accordance with previous studies. We believe that the decrease in TMP-SMX-related eruptions observed during the second ART period was a result of the introduction of combination ART, which decreased the need for chemoprophylaxis.

Lipodystrophy peaked during 1998–2006. Combination ART was introduced in Greece in 1996 and recording of lipodystrophy began in 1998. Lipodystrophy is known to be a metabolic evolutionary process and it is hard to determine the exact time of its appearance with stavudine; PI use was considered the most common cause in our study.

During the third ART period, we witnessed the introduction of newer PIs (darunavir, atazanavir) and integrase inhibitors with enhanced efficacy compared to older generation antiretroviral drugs. Furthermore, they seemed to be associated with a lower rate of lipodystrophy [16].

It is worth mentioning that in our study, zidovudine does not seem to be the main reason for clinical lipodystrophy despite its wide use for more than 20 years in Greece.

Other well-established studies have shown that thymidine analogues of nucleoside reverse transcriptase inhibitors (NRTIs) such as d4T and AZT are associated with lipodystrophy more often than PIs. NRTIs and PIs interfere with the metabolic process by causing mitochondrial dysfunction and oxidative stress, which in turn alters lipolysis, adipogenesis and glucose transport [17–20].

Skin reactions (MPs and Lyell's syndrome) associated with TMP-SMX occurred generally at low CD4 T cell counts (mean 166.5 cells/mm^3) and high viral loads (mean 358,698 HIV-1 copies/mL) when the drug was used as chemoprophylaxis in immunocompromised patients. Low CD4 T cell counts and increased interferon-gamma levels may contribute to the development of severe skin reactions like Lyell's syndrome [6,21].

During the more recent ART period, the newer regimens seem to cause fewer side effects while maintaining virological efficacy. Our hypothesis was confirmed by the decreased incidence of skin reactions when newer NNRTI-based ART regimens were introduced during the third period of our study. Next generation agents like PIs (atazanavir, darunavir), NNRTIs (rilpivirine, etravirine) and integrase inhibitors (raltegravir) are generally considered to have an improved safety profile [5,9,22].

We are aware of the limitations of this study due to the retrospective collection of data from patient files. Furthermore, some conditions may not have been correctly assigned to a particular drug or not recorded.

In conclusion, the major overall positive impact of ART has been associated over time, as in our study, with dermatological drug reactions including lipodystrophy and maculopapular eruptions. Their incidence since 2007 has been decreasing in association with changes in therapy. We believe that the constant improvement and introduction of new drugs in clinical practice will still require careful monitoring for skin reactions.

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Declaration of interest

All authors declare no conflict of interest.

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