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A retrospective study on the antiretroviral drug dispensing and adherence of the Hungarian HIV infected population

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Background

The **HEARTS** (***HIV Epidemiology and AntiRetroviral Treatment Study)*** was a non-interventional retrospective claims database study. The first results of HEARTS about the epidemiology of HIV patients in Hungary were published earlier. [1] In this part of the study, we analyse the antiretroviral treatment (ART) patterns.

An antiretroviral (ARV) regimen for a treatment-naive patient generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with a third active ARV drug from one of three drug classes: an integrase inhibitor (II), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a pharmacokinetic enhancer (booster) (cobicistat or ritonavir). [2]

According to WHO's guideline, the first-line ART should consists of 2 NRTIs and an NNRTI. [3] The European AIDS Clinical Society (EACS) recommends 2 NRTIs and an II, an NNRTI or a PI/r as initial treatment. [4] In contrast to these, there is no specific guidance for the third component of the ART in Hungary. [5]

Objective

Our aim was to investigate the changes of ARV drug dispensing over time at active substance and drug class level, to determine the therapeutic adherence of patients and examine the treatment duration of active substances as third agents of combination therapies, especially darunavir.

Methods

Data sources
- In Hungary, the National Health Insurance Fund (NHIF) longitudinally collects real-word data and records it in a database
- The NHIF database contains public-funded healthcare interventions and procedures
- Hungarian laws grant public access to data

Determination of HIV population
- Time frame: 1st January 2005 – 31st December 2015
- The study population was identified from the NHIF databases based on multiple inclusion criteria such as International Classification of Diseases (B20* - B24*, F0240, Z21H0, Z7170), International Classification of Procedures in Medicine codes (25568) and ARV medication purchase data
- We consider patients prevalent if they had their HIV viral count (ICPM: 25568) tested (n=1,772) [1]
- First, we analyse market share per active substances in treated prevalent population, who dispensed ARV drugs at least once between 2005 and 2015 (n=1,496)

Treatment patterns analysis' target population

If an HIV patient
- between 1st July 2005 and 31st December 2015
- purchased ARV drugs at least 2 times
- and the purchased drugs classified as non-NRTI (but NNRTI, PI, II, fusion inhibitor (FI) or entry inhibitor (EI))

he/she was included in the treatment pattern analysis (n=1,320)

Adherent HIV population

We calculated proportion of days covered (PDC) ratio in percentage as the quotient of
- the number of days while we assumed that patients are taking non-NRTI drugs was based on the date of drug purchasing, the dispensed quantity and days of treatment (DOT) of medication (numerator)
- and the number of days from the initial date of any ARV drug purchasing to the date of death or the end of follow-up (denominator)

A patient is consider to be adherent, if 80%≤ PDC ≤100% (n=1,055) [6]

Definition of treatment duration

We calculated treatement durations
- based on the adherent HIV population
- considering only 3rd agent drug classes (PI, NNRTI, II; number of patients=1,017) and active substances
- regarding the first dispensed drug during the time frame.

We compared only first-line ARTs.

Limitations

Invoking institutional privacy policies, the NHIF provides cumulative statistics only for categories comprising of at least 10 cases. This publishing practice limits the available dataset on number of patients who treated other therapy as a first-line treatment.

Information on the treatment of the study population is somewhat limited, since drug dispensing data afferent to in-patient care are not recorded in the NHIF database. And it is also possible that the treatment recorded first is not a first-line therapy (e.g a patient did not take any medication prior to the study period). Nevertheless, this is thought to have minimal impact on the cumulative drug utilization ratios observed in this study.

We calculated the adherence and the treatment duration based on the purchase data. We have no information on whether the patients actually took their medication or not.

Prophylactic and active treaments can not be distinguished.

Results

Market share per active substances in prevalent, treated population

We analysed the medical records of prevalent patients, who dispensed ARV drugs at least once between 2005 and 2015 (84.4% of prevalent patients, n=1,496). As expected, NRTI backbone had the highest market share during the total study period (Lamivudine: 62.1% [distinct patient number (n)=929], Tenofovir: 55.6% [n=832], Zidovudine+Lamivudine fix combination: 41.2% [n=617], results are not shown). [1] Among non-NRTIs, the most frequently purchased drug classes were PI (Darunavir: 27.6% [n=413], Lopinavir+Ritonavir fix combination: 25.7% [n=385]), NNRTI (Rilpivirin: 19.5% [n=292]) and II (Raltegravir: 15.3% [n=229], Dolutegravir: 11.7% [n=175]), respectively. Annual market share data presented in Figure 1 shows that the proportion of Darunavir and Rilpivirin usage have dramatically increased. Similarly, among the newer formulations (e.g. Raltegravir, Dolutegravir, 2 NRTI+Dolutegravir fix combination) we also found a significant growth during the study period.

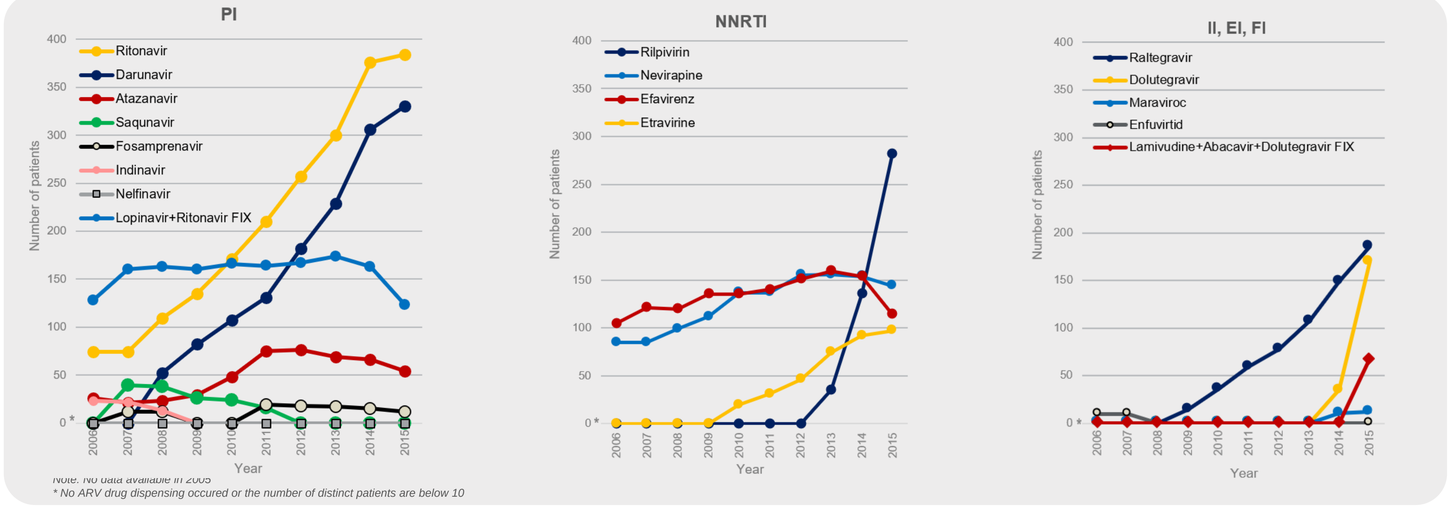

Figure 1. Annual market share per active substances by drug classes between 2006 and 2015

Proportion of adherent patients

We included patients in the treatment pattern analysis if they dispensed any drug, which classified as „non-NRTI" at least twice between 1st July 2005 and 31st December 2015 (n=1,320). Based on this population we assessed therapeutic adherence. Patients are facing the risk of treatment failure and the development of resistance mutations if their antiretroviral adherence and persistence is not optimal. According to early studies, viral suppression was only successful if the adherence was realtively high. Since then, this high level of required adherence is considered wrong by some. They say that with the improvement of regimens, it was observed that even with lower levels of adherence, viral suppression is possible. [7] In our study we found that proportion of adherent patients in Hungary assessed by the PDC ratio is 79,9% (n=1,055) (Figure 2).

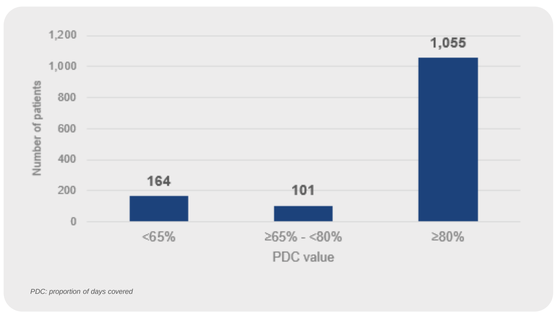

Figure 2. Number of adherent patients by PDC level

Treatment duration of selected drug classes as a first-line treatment among adherent patients

We studied the data of adherent patients (n=1,055) to calculate the treatment duration (ToT) of most commonly used first-line drug classes (NNRTI, PI and II) and selected active substances. For the full study period, we compared the most frequently dispensed active substances of each drug class (PI: DRV, II: Raltegravir, NNRTI: Efavirenz – which has been marketed around the same time as DRV). Out of adherent patients, 36 dispensed a regime which contains the three above mentioned drug classes in combination, or a different drug class such as EI or FI (Table 1).

The median treatment duration for NNRTI and PI was 7.91 years and 5.39 years, respectively. This suggests a significant difference between the treatment durations of NNRTI and PI based therapeutic strategies (p<0.0001). At 1 year, the proportion of patients still on treatment was 88.7% (86.1%-91.4%) for NNRTI and 87.9% (85.8%-90.1%) for PI, respectively. At 5 years, these values were 66.2% (61.7%-71.0%) for NNRTI and 51.9% (48.2%-55.9%) for PI (Table 2).

We analysed the treatment durations of Darunavir, Raltegravir and Efavirenz as the most commonly used substances within drug classes.The median treatment duration was 4.5 years for Darunavir and 6.2 years for Efavirenz (median has not been reached for Raltegravir). The 2-year ToT was 83.1% (78.5%-88.1%) for DRV, 75.3% (69.7%-81.4%) for Efavirenz and 72.8% (63.1%-84.0%) for Raltegravir.

Drug Class	No. Pts	Active substances	No. Pts
NNRTI	545	Nevirapin	173
		Efavirenz	171
		Rilpivirin	142
		Etravirin	33
		Combinations	***26***
PI	443	Lopinavir	183
		Darunavir	121
		Atazanavir	53
		Saquinavir	24
		Indinavir	15
		Nelfinavir	N/A
		Fosamprenavir	N/A
		Combinations	***32***
II	94	Raltegravir	67
		Dolutegravir	19
		Combinations	***N/A***

N/A: The number of distinct patients are below 10

Table 1. Number of adherent patients by first-line treatment

Drug Class	1-year ToT % (95% CI)	2-year ToT % (95% CI)	3-year ToT % (95% CI)	4-year ToT % (95% CI)	5-year ToT % (95% CI)
NNRTI	88.7 (86.1-91.4)	79.4 (76.0-83.1)	73.3 (69.4-77.5)	70.2 (66.1-74.7)	66.2 (61.7-71.0)
PI	87.9 (85.8-90.1)	78.3 (75.6-81.1)	64.6 (61.3-68.0)	58.3 (54.9-62.0)	51.9 (48.2-55.9)

CI: Confidence-interval; ToT: time on treatment

Table 2. Time on treatment by drug class

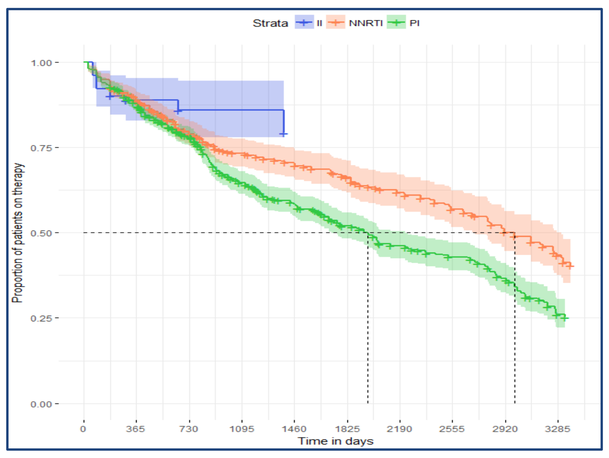

Figure 3. Treatment durations by drug classes as a first-line treatment

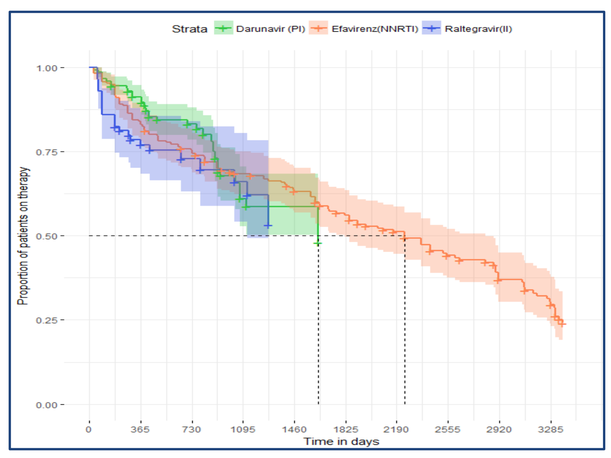

Figure 4. Treatment durations of the most frequently used active substances within drug classes as a first-line treatment

Conclusions

The present analysis is the second part of the HEARTS study, which is the a first retrospective longitudinal real-world data analysis of HIV patients in Hungary. In our study, we analysed the drug dispensing data of 1,320 HIV patients. According to our findings, the proportion of adherent patients (PDC ratio ≥ 80%) was 79,9% (n=1,055). These results show remarkable treatment adherence for the Hungarian HIV population included in our analysis.

The median treatment duration for NNRTI was 7.91 years and for PI 5.39 years, respectively. This suggests a significant difference between the treatment durations of NNRTI and PI based therapeutic strategies (p<0.0001). The 5-year ToT was 66.2% for NNRTI and 51.9% for PI.

We found considerable differences within the NNRTI drug class, namely the newer active substances, such as rilpivirin (available since 2013) offer better results in terms of treatment duration. Due to the development of ARV therapies and understanding their mechanism of action, we conclude that the tolerability and simplification of treatment administration could be major aspects of treatment success in real-world settings. Based on the results of our study, we conclude that the longest treatment durations can be achieved with NNRTI treatment regimens – as first-line therapies. We suggest the analysis of the subsequent use of these drug classes and active substances to be considered in the future.

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Research protocol received ethical approval from the ETT TUKEB under registration nr. 11444-2/2016/EKU (0205/16). The data reported here have not been presented previously.

Potential conflict of interest

Veronikai Halász, Péter Takács, Krzysztof Tronczynski, Inge Duchesne are employees of the Sponsor Janssen Pharmaceuticals. Katalin Kasza, Gabriella Merth, Gergő Merész, Péter Rózsa are employees of the independent consulting company MediConcept Ltd which received funding for contribution to the study design and data analyses. The fee for data extraction from the NHIF database has been covered by the Sponsor. János Szlávik has been an advisory board member/consultant/lecturer for or received research support from Janssen-Cilag, Gilead Sciences, MSD, and GSK.

Founding

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