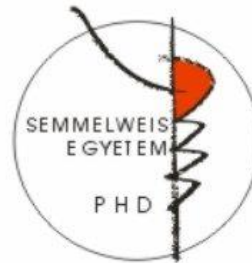# Current challenges in the care of human immunodeficiency virus infected patients: central nervous system disorders and drug-drug interactions

Doctoral (PhD) theses

Dr. Botond Lakatos

Semmelweis University
Doctoral School of Clinical Medicine

Supervisor: Dr. János Sinkó MD, PhD, honorary associate professor

Official reviewers:

      Dr. Gergely Kriván MD, PhD, Head

      Dr. György Lengyel PharmD, PhD, Head

Final Examination Committee:

Chair: Dr. László Timár MD, professor of medicine

Members: Dr. Gábor Pálos MD, PhD, associate professor

      Dr. Éva Karászi MD, PhD, Head

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1. INTRODUCTION

There has been rapid and dynamic development of antiretroviral treatment over the last three decades since 1983 when the human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome, was isolated. In the initial era of the HIV epidemic the goals were to manage opportunistic infections (OI) and malignancies, while the underlying infection progressed without any control. Once in widespread use antiretroviral treatment decreased the incidence of OI and malignancies, but the metabolic side effects of medicines became challenging. Regular administration of modern antiretroviral drugs enables excellent viral control. Furthermore, the dreadful side effects (lipodystrophy, metabolic syndrome, neuropathy, etc.) of former antiretrovirals are now minimised or eradicated all together with current regimes. Thus, the once feared "deadly" illness has become a well-controlled chronic disease.

According to data from the last decade life expectancy of HIV infected adults has risen dramatically and approach figures seen in normal population. Living with HIV is consequently now associated with more comorbidities and increasing polypharmacy leading to an increasing need for interdisciplinary communication and co-ordination. During regular care of HIV infected new problems and questions emerge challenging clinicians and scientists to look for appropriate answers.

This dissertation reviews the current challenges in the interdisciplinary care of HIV positive patients, specifically addressing central nervous system disorders and drug-drug interactions.

HIV and the central nervous system (CNS)

In parallel with the start of the HIV epidemic, case reports and epidemiological studies were published supporting the involvement of the CNS. One of the most common primary CNS manifestation of the virus, the AIDS dementia complex (ADC) had been observed in about 30-50% in the 1980s and 90s. ADC was characterized by multiform cognitive, motor and behavioural changes. Severe depletion of cellular immunity made the CNS vulnerable to opportunistic infections, which in turn resulted in additional harm. Morbidity and mortality due to neurological involvement was significantly higher in the

era before the implementation of combination antiretroviral therapy (cART). Even today, in the era of modern cART neurocognitive impairment among HIV patients is still present. The pathophysiological mechanism seems to be complex and several predisposing factors and contributing conditions are implicated. These phenomena is now termed as HIV-Associated Neurocognitive Disorders (HAND). Although the incidence of ADC has decreased dramatically, mild or asymptomatic disorders are still prevalent. Impairments with variable patterns in motor skills, memory, attention and mood provide differential diagnostic challenge for the clinician. There are three main forms of HIV related neurological disorders, namely primary complications, opportunistic infections and malignancies. HIV-associated motor and cognitive disorders arise with an estimated prevalence of 20% to 69%. To my knowledge no data from Central-Eastern Europe have been published before my theses. Survival of HIV patients with HAND are worse. Decreased self-care ability, quality of life and higher unemployment rates are reported more frequently, which might add to personal and social handicaps.

cART has an unambiguous role in reducing HIV-related neurological complications, particularly in terms of opportunistic infections and HIV-associated dementia. However, mild and asymptomatic neurocognitive disorders might still be observed as many as one in three patients. Prospective and non-controlled interventional studies have shown that antiretrovirals with better penetration into cerebral spinal fluid (CSF) might yield a more effective decrease in HIV ribonucleic acid (RNA) load. On the other hand several papers suggest neurotoxic effect of antiretrovirals. *Letendre* et al. described the relationship between CNS and antiretrovirals as a "double-edged sword". Antiretrovirals reaching insufficient concentration in the brain will not sufficiently control the viral replication within the CSF, while high concentrations of ARVs might cause neurotoxicity.

Drug-drug interactions of antiretrovirals

HIV patients on cART represent a high-risk group in the context of drug-drug interactions. 1. According to current scientific evidence, lifelong administration of triple combination of antiretrovirals is needed. 2. There are a number of new drugs for which there is not yet extensive clinical experience. 3. Management of opportunistic infections (i.e. tuberculosis), co-infections (i.e. hepatitis C) or malignancies require multiple and long-term coadministration of antimicrobials or chemotherapies. 4. Average life

expectancy of HIV patients approaches that of uninfected people, although often they have more comorbidities and more medicines to take. 5. Decentralized HIV care increase the chance of drug-drug interactions according to numerous authors.

Available observational studies show that as high as 20-30% of HIV patients on cART might take medicines with potential interactions and in 2-5% of cases absolutely contraindicated drugs are prescribed. Interactions may lead to reduced systemic exposure or - on the contrary - can yield higher tissue concentrations both with severe consequences. Suboptimal concentration of an antiretroviral will result in therapeutic failure and generation of resistant strains. Whereas overdosing can exaggerate the toxicities of antiretroviral.

2. OBJECTIVES

Aims of present research were as follows:

1. To identify prevalence and forms of neurocognitive disorders among Hungarian HIV infected patients.
2. To study risk factors among Hungarian HIV infected patients.
3. To assess correlations between antiretroviral use and neurocognitive impairment.
4. To investigate cerebrospinal fluid biomarker and neurocognitive pattern differences in triple antiretroviral therapy versus protease inhibitor monotherapy in international cooperation.
5. To study potential drug-drug interactions among Hungarian HIV infected patients and report a case.

3. PATIENTS AND METHODS

Clinical data, medication history and neurocognitive performance was assessed by a computerized neurocognitive battery of tests in the cohort of Hungarian HIV infected patients treated in the United Saint Istvan and Saint Laszlo Hospital between 2011 and 2012 were collected. Furthermore, the author participated in scientific collaborations and research projects in two HIV centers from abroad related to neurocognitive performance and drug-drug interactions. Volunteer participation of patients in studies has been certified by a signed written consent form. All studies were approved by local Ethical Committees.

3.1. Study to identify prevalence and forms of neurocognitive disorders among Hungarian HIV infected patients

Clinical and immunological data were collected, and medication and neurocognitive examinations were performed between May 2011 and August 2012 among Hungarian HIV patients regularly attending the HIV Outpatient Service of United Saint Istvan and Saint Laszlo Hospital. All adult (≥18 years) patients with confirmed HIV infection were offered to voluntarily participate in the national neurocognitive cohort-study. Patients were excluded if their general clinical condition was an obstacle to carry out test battery (severe tremor, Glasgow Coma Scale total score <15, current fever, neurodegenerative diseases in the medical history). A sensitive computerized neuropsychological battery of tests (Vienna Test System, Schuhfried GmbH, Mödling, Austria) was applied to assess neurocognitive performance. To obtain a representative sample, consecutive patients attending to medical checkup on defined days of the week were recruited. At enrollment, the patient's history was recorded and medical examination performed, followed by a detailed, validated neurocognitive performance battery of tests completed by all subjects. Functional quality of life was assessed by using MOS-SF36 test, while level of depression was screened by Beck Depression-Inventory Scale. Participants were asked to complete a structured questionnaire on life style (smoking habits, alcohol and drug consumption, sexuality). Neurocognitive performance was tested by six domains giving the ability to screen for and differentiate asymptomatic and mild neurocognitive disorders. Results were recorded using numerical parameters as well as figures. Subjects were classified based on T values, according to the algorithm of the American Society of Neurology

(Frascati criteria). Thus, patients were classified as showing no impairment, or having asymptomatic, mild or severe (dementia) neurocognitive impairment. Analysis was performed using SPSS version 21 software (SPSS Inc., Chicago, IL, USA). Patient characteristics, laboratory values and treatments were compared using the Chi-square or Fisher´s exact tests for categorical variables and the t-test or Mann-Whitney U test for continuous variables. For correlation measurements (raw scores) Pearson`s test was applied. Age- and education-matched validated normal values were available and implemented in the computerized program. A significance level of <0.05 was considered statistically significant.

3.2. Study to evaluate risk factors among Hungarian HIV infected patients

Methods and classification algorithms were carried out as described in section 3.1. Prospectively collected patient data was summarized in a spreadsheet program including the following details:

a. Duration of HIV infection
b. Stage of HIV at diagnosis, nadir CD4+T lymphocyte, viral load at the time diagnosis, start of treatment and at the time of examination; numbers and trend of CD4+ T lymphocyte values over all and at the time of examination.
c. cART treatment data; start, type and duration of treatment
d. Primary and cART-related comorbidities and coinfections (hepatitis C, hepatitis B, syphilis)
e. Quality of life, lifestyle, education, smoking, alcohol and drug consumption, earlier CNS diseases and mental illnesses based on questionnaires described in 3.1.

3.3. Study to assess correlations between antiretroviral use and neurocognitive impairment

HIV infected adult patients being on cART for at least 6 months before the neurocognitive examination were included in the analysis. Prospectively collected data on antiretroviral treatment were available at the Outpatient Service of the United Saint Istvan and Saint Laszlo Hospital. Detailed data on antiretroviral therapy were available for every patient

included in the study. Medication history was analysed for all antiretroviral classes and compounds. Separate duration of therapy for the most relevant antiretrovirals (protease inhibitors: atazanavir, darunavir, lopinavir; non-nucleosid reverse transcriptase inhibitors: efavirenz, etravirine, nevirapine; nucleoside reverse transcriptase inhibitors: tenofovir, zidovudine, abacavir, lamivudine) from the start of cART were subtracted. Duration and the Revised Central Nervous System Penetration-Effectiveness Ranking (CPE) scores of the different ARV regimens were calculated from the start of cART. For statistics we defined actual CPE score as of the ARV regimen at the time of neurocognitive evaluation, and cumulative CPE score as the time-proportional mean of CPE scores of each regimen during the entire cART interval.

3.4. Study to investigate cerebrospinal fluid biomarker and neurocognitive pattern differences in triple antiviral therapy versus protease inhibitor monotherapy in international cooperation

This cross-sectional analysis was a substudy of an observational single-center study comparing the prevalence of neurocognitive impairment in patients with fully supressed virus receiving protease inhibitors as triple drug therapy with nucleoside transcriptase inhibitors or as monotherapy (darunavir/ritonavir, lopinavir/ritonavir) carried out at the HIV Center of University Hospital La Paz, Madrid, Spain (Figure 1). Details of the parent study have been previously published. All patients who met criteria for neurocognitive impairment were offered to participate in the present substudy. In patients accepting enrolment CSF examination and plasma samples were obtained. CSF concentrations of following biomarkers were measured: adenosine deaminase, β2 microglobulin, neurone specific enolase, total tau protein, myelin basic protein, S100B protein and IgG Tibbling-Link index. For neurocognitive examination a psychologist blinded to treatment group conducted the assessment covering 7 domains. Neurocognitive impairment was defined following the American Association of Neurology 2007 criteria.
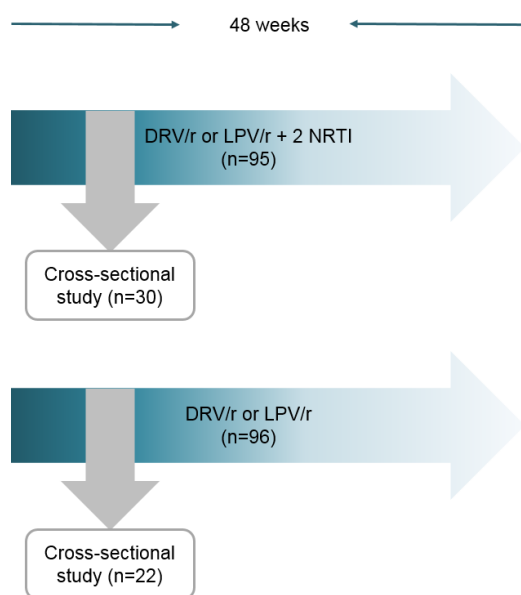
Figure 1. Comparative study of liquor biomarkers and neurocognitive pattern of patients with neurocognitive impairment receiving protease inhibitor monotherapy versus triple-drug antiretroviral therapy. DRV/r: darunavir/ritonavir booster, LPV/r: lopinavir/ritonavir booster, NRTI: nucleoside reverse transcriptase inhibitor

3.5. Study of potential drug-drug interactions among Hungarian HIV infected patients

In the present study HIV infected adult patients being on cART for at least 6 months before the neurocognitive examination were included – as specified in section 3.3. – to investigate potential drug-drug interactions. Source of data were derived from the prospectively collected medication history in the Hospital Patient Management System and prescribing software of the Outpatient Service. Medication prescribed at the Outpatient Service or administered during hospitalization were analysed for compounds and drug classes in a time-frame at neurocognitive examination ±3 months.

Administered medicines of each patient was evaluated using the database provided by Liverpool University HIV Pharmacology Group (www.hiv-druginteractions.org) and divided in to the following categories: no interaction expected, potential interaction, and coadministration is contraindicated as severe interaction is expected with the concurrent cART. In those cases where potential or severe interaction were observed, virological and immunological results were reviewed for the next 12 months. Transient vireamia (blips) and therapeutic failure for virological reasons were identified. Blips were defined as one detectable serum viral load <1000 copies/mL, and subsequently returning to undetectable

level without any modification of cART. While definition of therapeutic failure was defined as viral load>1000mL and a need for modification of cART.

4. RESULTS

4.1. Study to identify prevalence and forms of neurocognitive disorders among Hungarian HIV infected patients

A total of 123 HIV infected persons agreed to participate in the study. Two withdrew informed consent and 5 patients needed to be excluded due to lack of data.

Eventually 116 HIV infected individuals were enrolled (Figure 2); median age was 40 (IQR: 33-48) years, fifteen (13%) were women. Their median nadir CD4 cell count was found to be 223 (IQR:93-301) cells/ microliter. Mean time from diagnosis was 80 (IQR: 30-165) months. Altogether 106 persons were on antiretroviral therapy for a median of 48 (IQR: 24-172) months. 76% of them were supressed virologically at the time of evaluation.

Concerning comorbidities: 44% (51 patients) had hyperlipidaemia; 10 patients were coinfected with hepatitis B and five with hepatitis C; 29% of subjects had primary syphilis or a reinfection in the past 12 months. 47% of patients were smokers, 9% disclosed excess alcohol intake, whereas 6% admitted non-intravenous drug consumption.

HIV-associated dementia has been identified in two cases (1.7%) according to Frascati criteria. Mild (13 patients) and asymptomatic (23 patients) neurocognitive impairment accounted for 31% of the cases. In total 32.7% of individuals included in the study were identified as having neurocognitive impairment. Neurocognitive performance has been influenced negatively by severe depression in one patient, his case was not considered as having HAND.
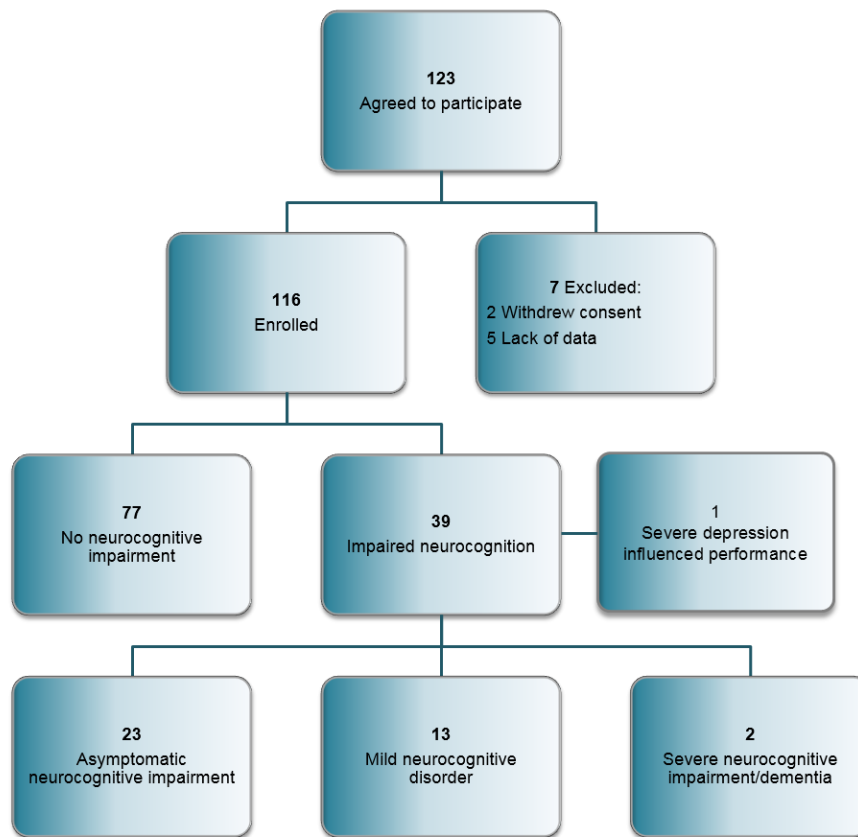
Figure 2. Flowchart of patients included in the study

4.2. Study to evaluate risk factors among Hungarian HIV infected patients

Demographic data were balanced between groups of patients with or without neurocognitive impairment. Patients with higher level (≥13 years) of education were significantly less disposed to develop a neurocognitive impairment (p=0.019). We found no significant differences in virological and immunological parameters, but observed a trend towards lower levels of nadir and actual (at the time of examination) CD4+ T lymphocyte count (p=0.14, p=0.12, respectively) among those with impairments. There were no significant differences related to coinfections (hepatitis C, hepatitis B, syphilis) or to hyperlipidaemia between the groups. Assessing the central nervous system, it was seen that stroke and psychiatric disorders were more common (p=0.025, p=0.029, respectively) in the group of patients with impairment. Smoking habits and alcohol consumption did not differ between groups. We found active drug use (stimulants in 4 patients, cannabis in 2 patients, cocaine in 1 patient) to be more frequent among patients with impairment. The average total score of self-reported patient-health survey (SF-36)

showed similar scores. In summary, CNS disorder in the past, psychiatric diseases and active drug use were found as predisposing factors, while higher level of education seemed to be protective.

Detailed analysis of neurocognitive tests correlating to selected demographic and immunological variables were studied. Lower nadir CD4+ T lymphocyte and lower CD4+ T lymphocytes measured at the time of examination revealed significant association with poorer performance in non-verbal learning test (p=0.038, p=0.013, respectively). Advanced age, longer infection history and longer duration of antiretroviral treatment were associated with worse visuo-motor results (p=0.003, p=0.007, p= 0.001, respectively).

Involvement of different domains in patients with neurocognitive impairment were as follows. Patients performed at least 1 standard deviation below the average: 29% by visuo-spatial memory test, 28% by fine motor test, 20% by non-verbal learning test, 17% by test of executive functions, 16% by visuo-motor test and 12% by measured reaction time.

4.3. Study to assess correlations between antiretroviral use and neurocognitive impairment

There were 89 individuals of the 116 enrolled patients who fulfilled inclusion criteria (on cART at least 6 months before the neurocognitive examination) for this substudy. The aim of this study was to assess correlations between antiretrovirals administered and frequency/pattern of neurocognitive impairments. At the time of examination 88% of cases were virologically undetectable. Demographics and immunological/virological data were balanced between the groups except for CD4+ T lymphocyte count (p=0.03) (Table 1). We observed a protective tendency of ZDV use at the time of examination (p=0.059), while TDF administration was significantly associated with neurocognitive impairment (p=0.037). In contrast, interestingly, length of ZDV, efavirenz (EFV) and lopinavir/ritonavir (LPV/r) administration showed a significant correlation with fine motor deficit (p=0.005, p=0.009 and p=0.007, respectively).

Table 1. Demographics and antiretroviral use of patients according to neurocognitive impairment (NCI).

	Patients without NCI (n=58)	Patients with NCI (n=31)	p value
Age. Mean (SD)	45 (±12)	43 (±10)	0.46
Male. N (%)	49 (84%)	27 (87%)	1.00
Undetectable viral load (<20 copies/ml). N (%)	51 (88%)	27 (87%)	1.00
Months of HIV infection. (SD)	105 (±67)	121 (±77)	0.30
Months of cART. (SD)	83 (±65)	102 (±67)	0.18
Nadir CD4+T cells/μl. (SD)	219 (±147)	189 (±125)	0.312
Mean CD4+T cells/μl at study period. (SD)	677 (±283)	541 (±260)	**0.03**
ZDV use at study period. N (%)	18 (31%)	4 (13%)	*0.059*
TDF use at study period. N (%)	15 (26%)	15 (48%)	**0.037**
EFV use at study period. N (%)	10 (17%)	6 (19%)	0.805
NVP use at study period. N (%)	12 (21%)	6 (19%)	0.881
NNRTI use at study period. N (%)	22 (38%)	12 (39%)	0.943
PI use at study period. N (%)	30 (52%)	14 (45%)	0.555

SD: standard deviation; HIV: human immunodeficiency virus; cART: combination antiretroviral therapy; ZDV: zidovudine, TDF: tenofovir, EFV: efavirenz, NVP: nevirapine, LPV: lopinavir/ritonavir, DRV: darunavir/ritonavir, ATV: atazanavir, NNRTI: non-nucleosid reverse transcriptase inhibitor, PI: protease inhibitor.

Actual CPE scores of cART at the time of examination were significantly lower in the group of patients with impairment (7.5 (SD: ±2.1; 95% CI: 6.9-8) vs. 6.5 (SD: ±2; 95% CI: 5.8-7.1); p=0.023). We found also a significant difference when calculating cumulative CPE scores (7.6 (SD: ±1.6; 95% CI:7.2-8) vs. 6.8 (SD: ±2; 95% CI: 6-7.5); p=0.031) (Figure 3).
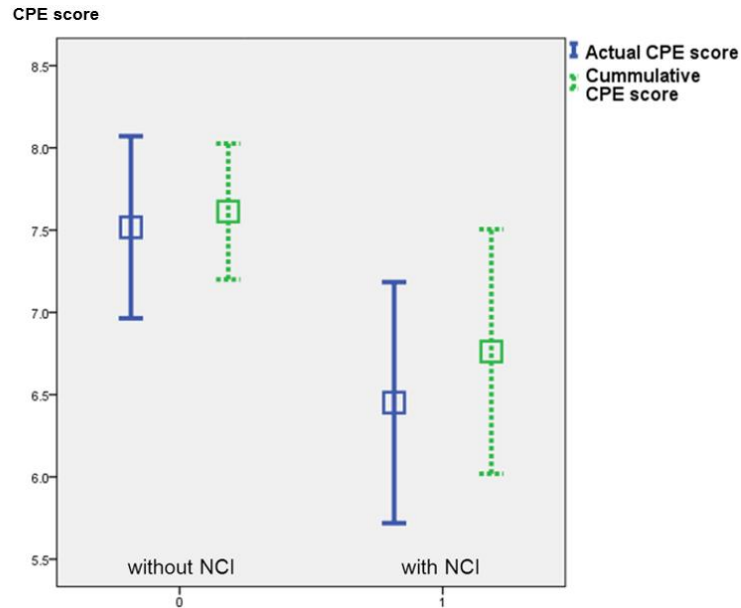
Figure 3. Actual and cumulative CPE scores according to neurocognitive impairment, n=89. Mean, 95% confidence interval. CPE: central nervous system penetration effectiveness; NCI: neurocognitive impairment

4.4. Study to investigate cerebrospinal fluid biomarker and neurocognitive pattern differences in triple antiviral therapy versus protease inhibitor monotherapy in international cooperation

We included 52 patients with neurocognitive impairment in the study performed at the University Hospital La Paz, Madrid. Patients receiving protease inhibitor monotherapy were older, had fewer years of education, had a longer duration of HIV infection and on-cART time and had a longer period of HIV viral load suppression. The prevalence of impaired neurocognitive domains were not statistically different between groups. There was a trend to more frequent impairment in the fine motor skills domain in patients receiving monotherapy. A total of 30 patients agreed and consented to have a lumbar puncture and CSF examination. A CSF viral load above 20 copies/mL was detected in one patient per group. The median levels of total protein and adenosine deaminase were slightly higher than upper limit of normal range in both groups. The median level of neurospecific enolase was greater than three times the upper limit of normal in both groups. We found no statistically significant differences in levels of other CSF biomarkers (Table 2).

Table 2. HIV-RNA detection and concentration of biomarkers in the cerebrospinal fluid of patients with neurocognitive impairment patients receiving triple drug therapy or protease inhibitor monotherapy

	Triple therapy (n=16)	Monotherapy (n=14)	p value
Detectable HIV RNA-Standard assay. N (%)	1 (6.3)	1 (7.1)	1.0
Detectable HIV RNA - Ultrasensitive assay. N (%)	8 (50.0)	10 (71.4)	0.28
White blood cells <5 cells/μl. N (%)	16 (100)	14 (100)	0.85
Total protein, mg/l. Median (IQR)	350 (262-524)	353 (265-374)	0.47
Total tau protein, pg/ml. Median (IQR)	185 (105-257)	177 (103-311)	0.83
Myelin basic protein, ng/ml. Median (IQR)	0.7 (0.4-0.9)	0.9 (0.4-1.6)	0.68
Neurospecific enolase, ng/ml. Median (IQR)	26.9 (15.0-32.8)	26 (23.6-32.3)	0.65
Tibbling-Link IgG. Median (IQR)	0.7 (0.5-1.3)	0.6 (0.5-0.7)	0.32
$\beta 2$ microglobulin, mg/l. Median (IQR)	2 (1-2)	1 (1-2)	0.58
S100B protein, pg/mL (IQR)	246.8 (171-287.3)	252.4 (199.7-280-2)	0.79
Adenosine-deaminase, U/l. Median (IQR)	4.7 (3.7-5.1)	4.8 (3.5-6.1)	0.91
HIV: human immunodeficiency virus, RNA: ribonucleic acid, IQR: interquartile range			

4.5. Study of potential drug-drug interactions among Hungarian HIV infected patients and a case report

In the present substudy 89 patients were enrolled, 13 (14.6%) of theme were females and the median age of patients was 43.6 (IQR: 36-52) years. Median nadir CD4 T+ lymphocyte count was 210 (IQR: 89-277) cells per microliter. Median infected time was 97 (IQR: 43-167) months and median cART use was 69 (IQR: 27-163) months. Altogether 70% of patients (62 persons) were taking at least one type of comedication, whereas 25% (22 persons) ≥3 comedications along with cART. Most common comedications were antimicrobials, followed by cardiovascular agents and central nervous system medications, proton-pump inhibitors and H2 receptor antagonists, lipid-lowering agents. We found potential drug-drug interactions in 27% of patients (24 persons) at the time of neurocognitive examination (±3 months), while 2 patients were taking comedication contraindicated with existing cART. In terms of cART, protease inhibitors were responsible for 15 cases of the potential or actual drug interactions, non-nucleosid reverse transcriptase inhibitors for 9 cases and nucleosid reverse transcriptase inhibitors only for one case (Table 3). Within 12 months after examination four patients

developed blips (<1000 copies/mL) and in three patients a therapeutic failure occurred, resulting in change of cART. In two cases a detectable viraemia was related to a straightforward adherence problem.

Table 3. Comedication administered along with antiretroviral therapy with potential interaction (orange) or contraindication (red)

Patient ID	Age (years)	ARV1	ARV2	ARV3	Comedication 1	Comedication 2	Comedication 3	Comedication 4	Comedication 5
1	60	3TC	ABC	ETR	atorvastatin	ciprofibrate			
2	43	3TC	ABC	LPV/r	clonazepam	berodual			
3	44	3TC	TDF	ATV/r	moxifloxacin				
4	28	3TC	TDF	DRV/r	ramipril	dapsone	spironolactone	furosemid	bisoprolol
5	60	3TC	ZDV	LPV/r	pantoprasol	nebivolol	doxazosine	furosemid	ferrous sulfate
6	45	3TC	ABC	NVP	bisoprolol	valproate	aciclovir	zopiclone	pantoprasol
7	50	3TC	TDF	LPV/r	phenytoin	carbamazepine	clonazepam		
8	35	3TC	ZDV	NVP	tiapride	tramadol	aciclovir	alprazolam	
9	47	3TC	ddI	LPV/r	famotidine	niflumic acid	clonazepam		
10	52	3TC	TDF	DRV/r	clonazepam	mirtazapine	ciprofibrate	doxycilince	cataflam
11	59	3TC	TDF	NVP	tramadol				
12	45	3TC	TDF	ATV/r	valproate				
13	75	3TC	ABC	LPV/r	metoprolol	fenofibrate	lansoprasole	ramipril	tramadol
14	64	3TC	TDF	DRV/R	atorvastatin	pantoprasol	tolperizon	enalapril	clopidogrel
15	65	3TC	TDF	DRV/r	coamoxiclav	tramadol	fluconazole		
16	45	3TC	TDF	ATV/r	famotidine	pantoprasol			
17	36	3TC	ZDV	EFV	amilorid	bisoprolol			
18	56	3TC	ZDV	EFV	acenocumarole				
19	38	3TC	TDF	DRV/r	famotidine	dapson	naproxen		
20	43	3TC	ZDV	ATV/r	diphenoxylate/atropine	tramadol	azithromycin		
21	45	3TC	TDF	NVP	zolpidem				
22	54	3TC	ZDV	NVP	amlodipin				
23	59	3TC	TDF	DRV/r	alprazolam	midazolam	fluconazole	ciprofloxacin	
24	53	3TC	EFV	LPV/r	aceclofenac	metoprolol	enalapril		

Light blue colours represent patients with blips; violet-coloured boxes refer to therapeutic failures with modification in cART; yellow coding shows non-adherent patients. ARV: antiretroviral, 3TC: lamivudine, ABC: abacavir, ETR: etravirine, TDF: tenofovir, LPV/r: lopinavir/ritonavir, ATV/r: atazanavir/ritonavir, DRV/r: darunavir/ritonavir, NVP: nevirapine, EFV: efavirenz

Along with my colleagues from University Hospital Basel we were the first to report a drug interaction between a protease inhibitor containing cART regimen and a direct factor Xa inhibitor resulting in a complication. The use of rivaroxaban in fixed dosing regimens without a need for routine coagulation monitoring may lead to the misconception that the risk of drug-drug interactions would be minimal. We described the case of a patient infected with HIV on salvage therapy who developed gastrointestinal bleeding while receiving the standard dose of rivaroxaban for the prevention of venous thromboembolism after surgery. This case clearly sends a warning that protease inhibitors should not be coadministered with rivaroxaban. Furthermore, it highlights the importance of clinicians' caution about potential drug-drug interactions.

5. CONCLUSIONS

Along with my co-workers I studied current interdisciplinary challenges in the care of HIV infected patients, with a specific focus on motor-cognitive disorders and drug-drug interactions.

1. Similarly to other developed countries, in about one-third (32.7%) of included patients a neurocognitive disorder was detected. To our knowledge, we were the first to report prevalence data from Central-Eastern Europe. HIV-associated dementia is a rare condition in Hungary but still exist.

2. Active drug consumption, a history of stroke, psychiatric diseases and lower CD4+ T lymphocyte count as well as lower level of education were risk factors for developing neurocognitive disorders. Most common forms of impairment were that of visuo-spatial memory and of fine motor skills.

3. In our cohort, both higher actual and cumulative CPE score values were associated with significantly better neurocognitive performance (p=0.03). However, duration of higher CPE score and certain ARV use (ZDV, EFV and LPV/r) was significantly associated with fine motor skill deficit in visuomotor or reaction time performance, suggesting neurotoxicity. These findings support the therapeutic-window concern of ARVs in the central nervous system.

4. We have shown within the Spanish research team's cohort, that if a patient develops neurocognitive impairment in the setting of undetectable HIV suppression in plasma (either on triple cART or on monotherapy), the severity of neurocognitive impairment, the concentration of biomarkers in CSF and the rates of HIV-RNA detection in CSF are not related to the number of antiretrovirals that the patient is receiving.

5. In a cross-sectional study of our cohort we found that potential drug-drug interactions might occur in about 20% of patients, and rarely severe interactions are also present. We were the first to report a drug interaction of protease inhibitor containing cART regimen and direct factor Xa inhibitor resulting in gastrointestinal bleeding. Antiretrovirals and

other drugs metabolized via the cytochrome P450 enzyme system might lead to interactions, thus caution is needed to avoid complications.

6. PUBLICATIONS

6.1. List of publications related to present theses

1. **Lakatos B**, Szabó Zs, Bozzai B, Bánhegyi D, Gazdag G: HIV fertőzött személyek neurokognitív eltérései – hazai prevalencia vizsgálat előzetes eredményei. Ideggyogy Sz. 2014;67:409-14.

2. Estébanez M, Stella-Ascariz N, Mingorance J, Pérez-Valero I, González-Baeza A, Bayón C, **Lakatos B**, Borobia A, Arnalich F, Arribas JR. A comparative study of neurocognitively impaired patients receiving protease inhibitor monotherapy or triple-drug antiretroviral therapy. J Acquir Immune Defic Syndr. 2014;67:419-23

3. **Lakatos B**, Stoeckle M, Elzi L, Battegay M, Marzolini C. Gastrointestinal bleeding associated with rivaroxaban administration in a treated patient infected with human immunodeficiency virus. Swiss Med Wkly. 2014 Jan 22;144:w13906

6.2. List of abstracts related to present theses

1. **Lakatos B**, Gazdag G, Szabó Zs, Bánhegyi D: Antiretroviral use and neurocognitive impairment – significance of the therapeutic window: experiences from a national cohort. Poster presented and published: EACS 2013, 14th European AIDS Conference, Brussels, Belgium; 16-19 Oct; Abstract book No.: PE-15/4, p.151.

2. **Lakatos B**, Gazdag G, Szabó Zs, Bánhegyi D: Prevalence and risk factors of HIV-associated neurocognitive impairment in a national adult HIV cohort in Hungary. Poster presented: IAS 2013, 7th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Kuala Lumpur, Malaysia; 1-3 Jul; Abstract No.: MOPE086.

6.3. Other publications

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