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Assessment of neurocognitive and motor functions in heavily treated HIV patients in comparison to patients receiving first line therapy only

Dissertation

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Zusammenfassung

HIV bleibt auch im 21. Jahrhundert eines der weltweit bedeutendsten Gesundheitsthemen. Seit der Entdeckung des Virus in den frühen 1980er Jahren haben sich Diagnostik und Therapieoptionen deutlich verbessert. Weiterhin ist jedoch weder eine Heilung möglich, noch existiert eine Impfung. Mit Hilfe einer medikamentösen Behandlung, die aus mehreren antiretroviralen Substanzen besteht, kann die HIV-Infektion jedoch zu einer kontrollierbaren, chronischen Erkrankung werden. Durch die länger werdende Lebenserwartung von HIV-Patienten muss das Management von Medikation, Nebenwirkungen und langfristigen Folgen und Erkrankungen in den zentralen Fokus von Forschung und Medizin rücken. Ein wichtiger Aspekt ist hierbei die HIV-assoziierte neurokognitive Störung, ein Symptomkomplex, der circa 25-50 % der HIV-Patienten betrifft. Neurokognitive Einschränkungen scheinen in ihrer Inzidenz zunehmend zu sein, auch unter adäquater Ersttherapie. Ein weiterer Aspekt ist das Therapieversagen der Ersttherapie. Im langfristigen Verlauf spielt die Entwicklung von Resistenzen oder Intoleranzen eine relevante Rolle. Dies betrifft insbesondere die Gruppe der sogenannten „heavily treated patients“, eine Subgruppe an HIV-Patienten die intensivierte antiretrovirale Therapie benötigen, um eine adäquate Viruskontrolle zu erreichen. Diese intensivierte Therapie bringt jedoch eine Vielzahl an Herausforderungen mit sich und verkompliziert das Management für Patienten, Behandler und Forschende.
Aufgrund dieser komplexen Situation und des Status als Minorität ist die Datenlage in Bezug auf die Subgruppe der „heavily treated patients“ gering und mehr Forschung dringend notwendig.

Diese Arbeit exploriert die Unterschiede und Gemeinsamkeiten von „heavily treated patients“ im Vergleich zu HIV-Patienten, die Ersttherapie erhalten, im Hinblick auf ihren neurokognitiven Status. Beide Patientengruppen durchliefen eine Reihe von neurokognitiven und motorischen Tests. Die Tests umfassten verbale, exekutive und motorische Funktionen sowie die Informationsverarbeitungsgeschwindigkeit. Im Anschluss wurden dieses Daten für globale Skalen und Untertests statistisch ausgewertet.

Zusammenfassend lässt sich sagen, dass sich beide Gruppen nur marginal unterscheiden. „Heavily treated patients“ scheinen im Vergleich zu HIV-Patienten unter Erstlinientherapie ein leicht vermehrtes Defizit in motorischen Funktionen aufzuweisen. Bei näherer Betrachtung zeigt sich ein komplexes Bild der Leistungen dieser Subgruppe, mit Defiziten vor allem in einzelnen Leistungsbereichen.
Insgesamt erreichten beide Gruppen vergleichbare Ergebnisse. Dies lässt darauf schließen, dass die Gruppe der „heavily treated patients“ von der intensivierten Therapie profitiert und trotz fortgeschrittener Erkrankung und zusätzlichen Nebenwirkungen die neurokognitive und motorische Leistungsfähigkeit erhalten bleiben.

Abstract

HIV remains one of the most relevant health issues on a global scale. Since the discovery of the virus in the early 1980's diagnostic and therapy options have improved significantly; however, a vaccination or cure does not exist. With a treatment consisting of multiple antiretroviral substances taken daily, the potentially deadly infection can be converted into a manageable, chronic disease. Due to the increasing life span of HIV patients, the management of medication, side effects and long-term health consequences has become the focus of science and medicine. One important issue is the development of HIV associated neurocognitive disorder, a syndrome affecting about 25-50 % of all HIV positive patients. Neurocognitive impairment seems to be increasing in incidence, even in patients on first-line treatment. Another rising issue is the failure of first-line treatment. In long-term treatment, development of resistances or intolerances might become of concern. This applies to the group of heavily treated patients, a minority within the HIV population that has increased medication needs to achieve adequate disease control. Intensification of treatment, however, entails several challenges and complicates disease management for the patient as well as for their doctors and the scientific community.
Due to this complexity and the minority status, research regarding this subgroup is scarce.

This thesis´ aim is to explore the differences and similarities of heavily treated patients in comparison with HIV patients receiving first line therapy regarding their neurocognitive status and performance.
Both patient groups completed a series of neurocognitive and motor testing. This includes testing of verbal, executive and motor function as well as information processing. Subsequently, the results were statistically analyzed on a global level and for the subtests.

In summary, the results showed only a slight difference between both groups. Heavily treated patients seem to exhibit an increased deficit in motor function in comparison with HIV patients treated with first-line therapy. However, analysis revealed a rather complex composition of heavily treated patients.
On an overall level, both groups achieved comparable results. The findings of a similar clinical outcome for the heavily treated patients indicates a benefit from the intensified medication approach. Despite increased side effects and challenges that this treatment intensification entails, it seems to lead to an improvement in quality of life.

Abbreviations/Abkürzungsverzeichnis

3TC	Lamivudin
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
AM	Amplitude of force
ANI	Asymptomatic neurocognitive impairment
AZT	Zidovudine
cART	Combined antiretroviral therapy
CCR5	C-C chemokine receptor type 5
CD4+ T cell	Cluster of Differentiation 4 positive T Cell, T Helper Cell
CDC	Center for Disease Control
CMV	Cytomegalovirus
CNS	Central nervous system
CPE	CNS Penetrating Effectiveness
CSF	Cerebrospinal fluid
CT	Contraction time
CXCR4	C-X-C chemokine receptor type 4
DAIG	Deutsche AIDS Gesellschaft
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FTC	Emtricitabine
gp	Glycoprotein
GRID	Gay-related immune deficiency
HAD	HIV-1 associated dementia
HAND	HIV associated neurocognitive disorder
HAWIE	Hamburger Wechsler Intelligenz Test für Erwachsene
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-lymphotropic virus
HTP	Heavily Treated Patients
IL-1	Interleukin 1

INI	Integrase inhibitor
kHz	Kilo Hertz
LAV	Lymphadenopathy-associated virus
ml	Milliliter
ms	Millisecond
MHC	Major histocompatibility complex
MND	mild neurocognitive disorder
MRC	Most rapid voluntary isometric index finger extension
MRAM	Most rapid alternating movement
MSM	Men who have sex with men
MWT-b	Mehrfach Wortwahl Test-b
N	Newton
NAT	Nucleic acid test
NFAT	Nuclear factor of activated T-cells
NFkB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Nm	Newton meter
NNRTI	Non-nucleoside reverse-transcriptase inhibitors
NO	Nitrogen oxide
NRTI	Nucleoside reverse-transcriptase inhibitors
PML	Progressive multifocal leukoencephalopathy
PCR	Polymerase chain reaction
PI	Protease inhibitor
RNA	Ribonucleic acid
RRT	Rate of rise of tension (RRT = AM/CT)
RT	Reaction Time
SIVcpz	Simian immunodeficiency virus in chimpanzees
SIVsm	Simian immunodeficiency virus in sooty mangabeys
STI	sexually transmitted infection
TAF	Tenofovir-Alefenamide
TasP	Treatment as Prevention
TDF	Tenofovir disoproxil
TMT	Trail Making Test
TNF alpha	Tumor necrosis factor alpha
UN	United Nations

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1. Introduction

1.1. Historic Development

1.1.1. Discovery

The Acquired Immune Deficiency Syndrome (AIDS) was discovered in the United States of America in the early 1980s. However, HIV (human immunodeficiency virus), the virus responsible, has been detected later on in blood samples dated as early as 1959 (Zhu et al., 1998).

In 1981, the earliest AIDS cases emerged. The Center for Disease Control (CDC) reported five young male patients presenting with symptoms of pneumocystis carinii pneumonia (known today as Pneumocystis jirovecci), usually found only in immunocompromised patients. All these patients additionally suffered from candida infections and were tested positive for cytomegalovirus (CMV). Furthermore, three patients had experienced fever for several months, and three of them showed severely decreased numbers of lymphocytes. The patients had no personal connections, yet all of them reported drug abuse, one using intravenous (i.v.) drugs and two of the patients were homosexual (Gottlieb, 1981).

Similar cases, often associated with lymphadenopathy, occurred. In addition, a striking accumulation of patients with the rare Kaposi's sarcoma was identified (Friedman-Kien, 1981). It was obvious that the new disease compromised the immune system, and, it was hypothesized first, that a new CMV strain might have emerged. However, the possibility of an unknown agent causing immunodepression with a resulting CMV infection was also discussed.

Frequent features of the affected group appeared to be homosexuality, intravenous drug use, and hemophilia, while a substantial number of recorded cases seemed to be geographically related to Haiti. Taking these observations into consideration, blood transfusion and sexual contact were suggested to be the most likely mode of transmission (CDC, 1982a; Cohen, 2006; Gilman, 1987).

There was no official name for the new and complex disease, but descriptive terms referencing symptoms or associated characteristics like "4H Disease" (for homosexual, heroin, Haiti, hemophilia) (Cohen, 2006) or "GRID" (Gay Related Immune Deficiency) appeared in literature (Altman, 1982). In 1982, the CDC implemented the term "AIDS" which is still used today (CDC, 1982b).

The virus was successfully isolated by two separate research groups in 1983, and both published their findings in the same issue of *Science*. Gallo et al. (1983) named the virus human T-lymphotropic virus III (HTLV-III) because of its similarity to the known lentivirus HTLV-I. The group around Barre-Sinoussi isolated the virus from a patient with enlarged lymph nodes and therefore called it lymphadenopathy-associated virus or LAV (Barre-Sinoussi et al., 1983). The virus was

renamed HIV in 1986 (Marx, 1986). Today, there are two known viruses effecting the human population, HIV-1 and HIV-2.

1.1.2. Origins of the virus

The most reliable findings regarding the origin of the HI virus indicate that it emerged from viruses in non-human primates being transferred to humans in West-Central Africa. HIV-1 seems to be a variant of the simian immunodeficiency virus SIVcpz that infects chimpanzees while HIV-2 is closely related to SIVsm which occurs mainly in sooty mangabeys (Reeves & Doms, 2002). SIV transmission likely occurred through contact to an infected monkey's blood or fluids, for example during the hunt (Marcia et al., 2005), or the preparation of bushmeat (Peeters et al., 2002). SIV infection itself, however, is only slightly pathogenic. SIV seems to have mutated during this cross-species transfer and thus, the more virulent HI virus developed. The transfer appears to have happened on several separate occasions, resulting in the HIV-1 subtypes M, N, O and P, with M being the most prevalent group (Sharp & Hahn, 2011).

1.1.3. Social and Economic Impact

In the early 1980s, little was known about the newly emerging disease AIDS and, understandably, people were frightened. Terms like the aforementioned GRID, as well as "gay cancer" and "gay plague" were used (Alert Citizens of Texas, 1983; Wright, 2006). The death toll was rising and yet the emerging crisis was ridiculed, even by the president of the United States of America at that time, Ronald Reagan (Calonico, 2015; Gibson, 2015). The earliest record of President Reagan mentioning AIDS publicly originates from 1985 (Boffey, 1985), and retrospectively, his administration's prolonged inaction was broadly criticized (Paules et al., 2017).
Today, many people living with AIDS encounter less prejudice than 35 years ago. However, stigma surrounding HIV remains a significant issue which still affects people's lives. Carrasco found stigma to be a barrier to HIV testing, counseling, access to therapy as well as a cause for an HIV positive person not to disclose their status either publicly or even to their partner (Carrasco et al., 2017). Another study associates the stigma with depression and social isolation (Rueda et al., 2016). In addition to the external stigma imposed by society, internalized stigma affects many HIV positive people as well (Baugher et al., 2017).

Children are a highly vulnerable group, due to becoming infected themselves or due to the consequences of HIV infections in their immediate families or community. Vertical transmissions, meaning the transmission from mother to child during pregnancy, birth or breastfeeding have

dropped significantly. Between 2010 and 2022 the number of vertical infections decreased by 58%. New HIV infections among children between the ages of 0 and 14 in 2022 were at an all-time low of 130.000 globally, the lowest number of new infections since the 1980s (UNAIDS, 2023b). In addition to contracting HIV, children are affected through their parents HIV infection or through becoming orphaned due to HIV related reasons. 2022 an estimated 13.9 million children between the ages of 0-17 years had lost one or both parents to HIV and AIDS (United States Agency for International Development, 2024). Loraine Mukazi, a speaker at a conference hosted by the European Commission and orphaned by AIDS herself expressed the experience in the following words (UNAIDS, 2011):

> "Being an AIDS orphan is to become an adult very quickly, a parent for your own parents, a head of a family (…) Losing a parent is already difficult, losing a parent to AIDS even more so, as you are confronted with the denial, taboo, stigma and countless questions."

HIV does not only impact the infected but their family and community as well. Treatment and support for communities, parents and people living with HIV has direct consequences for HIV-related orphans and vulnerable children. Therefore, programs like the US government's PEPFAR (President's Emergency Plan for AIDS Relief) aim for a systematic approach addressing poverty, education, equality and health care to reduce the populations vulnerability and strengthen communities (United States Agency for International Development, 2022).

The financial cost of HIV for society and the single patient has changed dramatically over the last three decades. While therapy options were limited in the early days, hospitalization over long periods of time was necessary, resulting in an inability to work. Both, health care costs and the loss of capacity to work, contributed to the financial costs of HIV. With the beginning of HAART (highly active antiretroviral therapy) in 1996 these factors changed for the better. Along with improved quality of life for the patients, time spent in the hospital was shortened and the costs reduced. Although life expectancy and therefore duration of expensive antiretroviral therapy has increased, the overall cost per patient has declined (Gonzalo et al., 2009). Additionally, within the last few years, patents on several antiretroviral substances have ended, resulting in open market competition and reduced prices for medication overall (Hoffmann, 2018). For the individual patient, however, costs of medication and treatment can still be detrimental, making adequate support systems necessary (Veenstra & Whiteside, 2005).

1.2. Epidemiology

HIV is a global epidemic, leading to many casualties and complications. Because of this immense impact on public health, the United Nations developed a 2030 plan to end the HIV epidemic (UNAIDS, 2014b). One of the main elements was the 90-90-90 treatment target. By 2020 the goal was for 90% of infected individuals to know their HIV-status, for 90% of those to receive treatment and for 90% of the treated individuals to achieve a suppressed viral load (UNAIDS, 2014a).

An updated report from 2021 reveals that most of these targets for 2020 have been missed worldwide (World Health Organisation, 2021). For example, instead of 90% of HIV positive people receiving treatment the report reduces this number to 73%. This setback can be in part attributed to the global pandemic with the SARS-Cov-2 virus which has bound immense financial, scientific, and human resources and made access to the available testing and treatment increasingly difficult.

The goal of eliminating HIV remains although the short-term plan is to get back on track and reimplement testing and treatment services as they existed before the Covid-19 pandemic hit.

In July 2022 the World Health Organization published an updated resolution (World Health Organisation, 2022). The targets include a reduction of the overall number of infected persons from 1,5 million in 2020 to 335.000 in 2030 and the 90-90-90 goal has been updated to a 95-95-95 target and to end the AIDS epidemic by 2030. A report by UNAIDS from 2023 states that several countries including Botswana, Eswatini, Rwanda, the United Republic of Tanzania and Zimbabwe have achieved the 95-95-95 target and others are close (UNAIDS, 2023b).

1.2.1. Global Data

The newest statistics available from the United Nations claim that globally 39 million people were living with HIV in 2022 (UNAIDS, 2023a). About 29.8 million of them (76%) had access to antiretroviral treatment, though the availability differed severely depending on the region. In 2022, there were 1.3 million new infections with HIV. The number of new infections has declined in both adults and children over the last years. The UN reports 1.5 million children (included in total number) living with HIV (UNAIDS, 2023a).

Worldwide, 630.000 people died of HIV and AIDS related illnesses in 2022. Since the beginning of the epidemic, estimated 40.4 million people lost their life due to the virus (UNAIDS, 2023a).

1.2.2. German Data

Exact numbers concerning HIV infections in Germany are not available but, based on algorithms and data from several registers, updated numbers are published by the German Robert Koch Institute (RKI). Data availability for 2022 is limited due to delayed publishing by the RKI, data shown below depict the years 2021 and 2022 (Robert Koch Institut, 2023).

At the end of 2021, an estimated number of 90.800 people in Germany were living with HIV, 8.600 of those undiagnosed. In 2021 there were 1800 new HIV infections. 96% of known infections were treated and 96% of treated infections had a suppressed viral load (Robert Koch Institut, 2022).

For the year 2022, there were approximately 1900 people who were newly infected with HIV. Of these newly infected individuals, 1.000 are men who have sex with men (MSM), 520 got infected through heterosexual intercourse (310 women, 210 men) and about 370 were infected through intravenous drug use (Robert Koch Institut, 2023).

The reported number of newly registered HIV infections for 2022 was 3.239. The discrepancy between the number of newly registered infections and the estimation of 1900 new infections can be explained by HIV positive Ukrainian refugees entering Germany in 2022. By law, every HIV infection, new or pre-existing, must be registered. A detailed statistic can be found in the RKI Bulletin 47/2023 (Robert Koch Institut, 2023).

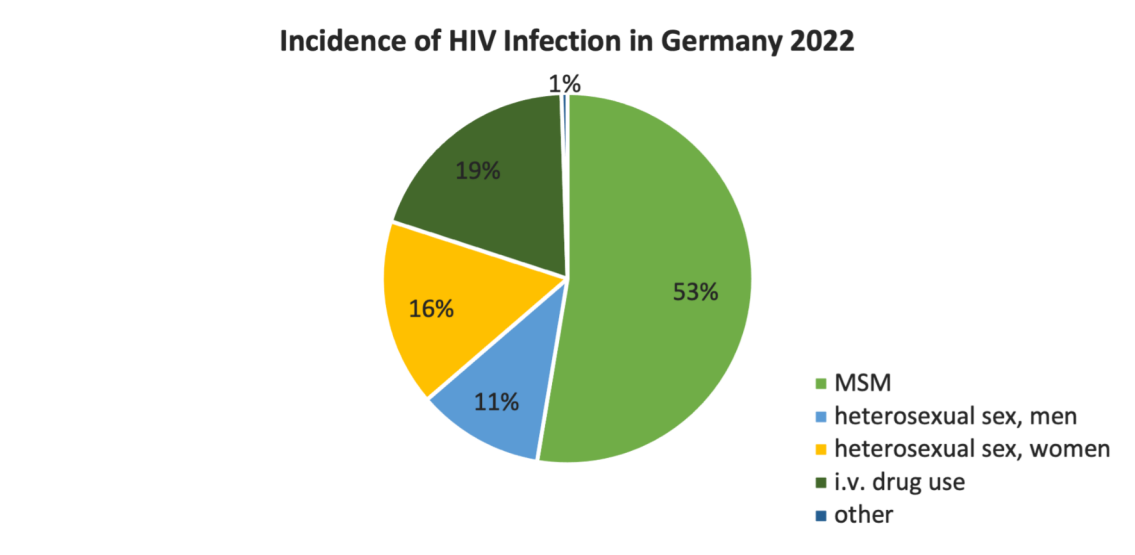

Fig. 1: **Incidence of HIV Infection in Germany 2022, according to data from Robert Koch Institut (2023)**

53% of newly acquired infections occurred in men who have sex with men (MSM), while 27% of new infections occurred through heterosexual intercourse with 16% women and 11% men. 9% of HIV transmissions were due to intravenous (i.v.) drug use. Perinatal, intrauterine and mother-to-child transmission has not occurred in Germany in 2022, though it is a relevant transmission mechanism globally.

In comparison with previous years, overall infections of 2022 were on the rise. MSM infections are lower while there is an upward trend in the heterosexual population as well as in infections transmitted through intravenous drug use.
New infections as well as the detection of new infections remain a challenge for the German health community and authorities.
In regard to the number of patients receiving therapy and the number of patients who are treated successfully (viral load < 200 copies/ml blood) Germany achieved the WHO's 95% goals (Robert Koch Institut, 2023). Treatment is recommended by the DAIG (Deutsche AIDS Gesellschaft) for every infected person since 2015 (Deutsche AIDS Gesellschaft e.V., 2017a).

1.3. The HI Virus

1.3.1. Classification

Human immunodeficiency virus is a lentivirus from the family of retroviruses. Two virus strains are known to be pathogenic for humans, HIV-1 and HIV-2. HIV-1 entails the groups M, N, O and P, which can be further subdivided. While subgroups O and N are mostly restricted to West African regions, M can be found worldwide and comprises subtypes A-F with subtype B being most common. HIV-2 on the other hand is a distinct virus that occurs mainly in West Africa, Mozambique, India and rarely in Portugal (which had previous colonial ties to Mozambique) (Schulz, 2009).

1.3.2. Genome and proteins

HI virus itself consists of a lipid membrane and a core, for an overview see figure 2. It measures 120 nm in diameter (Murphy & Weaver, 2017) and its overall shape resembles that of an icosahedron (20 triangular surfaces) (Renz-Polster & Krautzig, 2013).
On the surface of the lipid membrane so-called viral spikes can be found. A spike is a trimer consisting of the glycoprotein gp120, connected with the membrane by glycoprotein gp41 (Murphy & Weaver, 2017). Both proteins emerge from the proteolytic cleavage of gp160, which is encoded in the env (envelope) gene (Schulz, 2009). Gp120 interacts with the cell via the cell's CD4+ receptor, while gp41 enables the fusion of the cell and virus membrane (Murphy & Weaver, 2017). Gp120 furthermore entails a V3 loop which binds to the co-receptor of the cell (usually CCR5 or CXCR4) and therefore determines the virus' tropism (Dittmar et al., 1997). Inside the lipid membrane a matrix is formed by p17 (Schulz, 2009).

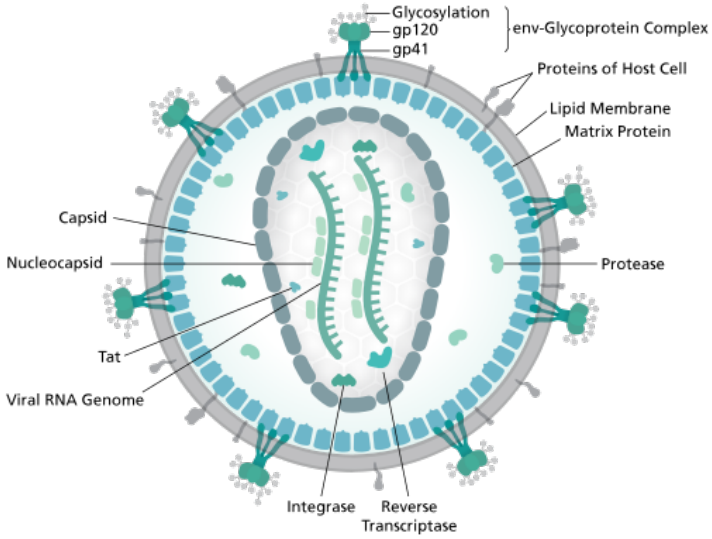

Fig. 2: **Structure of an HI virus**
The outer surface of the HI virion consists of trimeric spikes of gp120 and gp41 (glycoprotein). Inside a matrix layer can be found. The viral core consists of ca capsid which entails two strands of viral RNA (ribonucleic acid). Graphic made by Thomas Splettstoesser used under CC BY-SA 4.0 license.

The capsid consists of numerous copies of the protein p24. Inside, two ribonucleic acid (RNA) strands can be found, tightly connected to p6 and p7. Within the capsid, there are the virus protease, the reverse transcriptase and the integrase, three enzymes mandatory for viral replication (Schulz, 2009).

The genome consists of two of positive-sense single strand RNA, each containing 9193 nucleotides (Wain-Hobson et al., 1985). The 3' end includes a poly-A tail while the 5' end consists of a cap. The encoding region encompasses nine genes. The RNA's genes encode for enzymes, proteins and perform regulatory functions (Foley et al., 2018; Kuiken et al., 2008):

- gag (group specific antigen): encodes for the precursor protein p55 which is processed by the viral protease resulting in the proteins p6, p7, p17 and p24
- pol (polymerase): encodes for the viral protease, the reverse transcriptase, and the integrase which originate from a gag-pol precursor polyprotein which is processed by the viral protease
- env (envelope): encodes for the precursor protein gp160 which is processed to form the glycoproteins of the outer membrane, gp41 and gp120
- tat (transactivation of transcription): important viral regulatory factor, activates and controls transcription, first eukaryotic transcription factor known to interact with RNA

- rev (regulator of virion): important viral regulatory factor, promotes nuclear export, stabilization, and utilization of unspliced viral mRNA
- vif (virion infectivity factor): provides infectivity to virus particles, without it, particles are defective while cell-to-cell transmission remains intact
- vpr (viral protein r): interaction with precursor protein, several other functions are being discussed
- vpu (viral protein u): integral membrane protein unique to HIV-1 that plays a role in the degradation of CD4+ within the endoplasmatic reticulum and the release of virions from infected body cells
- nef (negative factor): multipurpose protein, involved in degradation of CD4+, maintenance of high viral load, increase of infectivity, progression to AIDS (in some long-term survivors of HIV-1 nef has been found to be defective or missing)

The encoding region of the RNA strand is flanked by two long terminal repeats at each end and includes two exons, one next to tat and one next to rev, which are spliced during the translation process (Foley et al., 2018). In some HIV strains an antisense open reading frame encoding an antisense protein was found. Its high retention suggests playing a role for the product but its exact function has not yet been identified (Foley et al., 2018).
To summarize, HI virus contains two strains of RNA with nine genes. Three of these genes encode for proteins and enzymes necessary for the replication process (gag, pol, env) while the other six perform regulatory functions.

1.3.3. Cycle of Replication

HI virus requires a cell of the host body to replicate (see figure 3), more specifically, a cell which expresses a CD4+ receptor (Dalgleish et al., 1984). These are CD4+ T cells, dendritic cells and macrophages. First, the virion engages with the CD4+ receptor with its gp120 glycoprotein. Upon contact, the glycoprotein 120 undergoes a conformity change, exposing the V3 loop which is able to interact with a chemokine co-receptor of the host cell (Bour et al., 1995). There are two known types of co-receptors, CCR5 and CXCR4. While CCR5 is mainly found on effector memory CD4+ T cells, dendritic cells and macrophages, CXCR4 is expressed by naïve CD4+ T cells and central memory CD4+ T cells. This distribution of co-receptors plays an important role for the rate and mode of transmission as well as for the virus' propagation within the infected host cell (Murphy & Weaver, 2017). The exact structure of the V3 loop determines the tropism of the virus, i.e. the type of co-receptor to which the virus can bind and thus which cell type is mainly affected by the

HI virus (Jiang et al., 2017). Once the gp120 has bound to the co-receptor, the trimeric spike, consisting of gp120 and gp41, dissolves and a fusion domain on gp41 is exposed. Upon contact of the fusion domain with the cell's membrane, both membranes partly dissolve, and the virus capsid can enter the cytoplasm (Schulz, 2009).

Inside the body cell, the capsid disintegrates. The contents of the capsid, specifically p17, the reverse transcriptase and the virus RNA form the pre-integration complex. The complex is transported into the cell's nucleus. During the transport, RNA is transcribed into DNA by the viral reverse transcriptase.

First, a tRNA binds to the primer binding site between the long terminal repeat and gag close to the 5' end. The reverse transcriptase synthesizes a short DNA sequence in 5' direction. This sequences docks onto the matching segment at the 3' end and now serves as a primer for the transcription in 3' to 5' direction (Schulz, 2009).

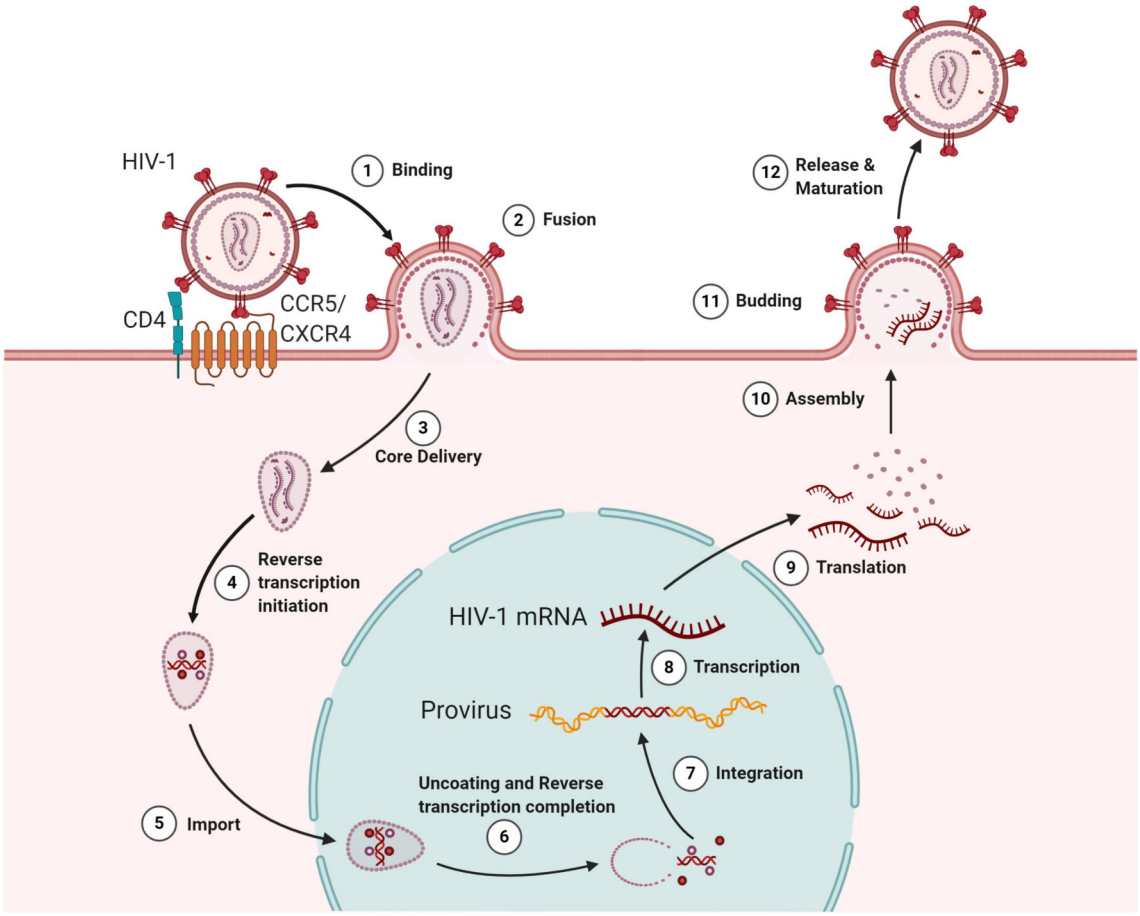

Fig. 3: **Replication Cycle**

The virus attaches to the cell and is then incorporated causing the capsid to dissolve. The viral RNA is transcribed by the viral reverse transcriptase, resulting in viral DNA. Inside the cell's core, viral DNA is integrated into the cell's DNA by viral integrase. Through transcription by the cell's polymerase new viral proteins and RNA are synthesized, packaged into new virions, and released from the cell. Graphic by Ramdas et al. (2020) used under CC BY 4.0 license.

Through the docking of the integrase onto the newly synthesized DNA strand, a pre-integration complex is formed. Both ends of the viral DNA are replaced with 3'hydroxyl groups. Once inside the core, these 3' hydroxyl groups bind to the phosphodiesters of the host DNA and both strands merge, aided by the host cell's repair enzyme (Lataillade & Kozal, 2006; Liao et al., 2010)**.** The integrated DNA segment is called "provirus" (Murphy & Weaver, 2017). This fusion of DNA enables the virus' persistence within the cell, and therefore within the patient, over long periods of time (Chun et al., 1997).

Now that the virus DNA is integrated into the cell's genome it can be read and transcribed by the cell's DNA polymerase II, resulting in mRNA. This RNA exits the nucleus and can either be directly implemented into new virions or translated into proteins and enzymes. The capsid RNA is translated by the free ribosomes while the precursor protein gp160 is translated by either the Golgi apparatus or in the endoplasmic reticulum (Schulz, 2009) and later cleaved into gp120 and gp41 by a protease of the host cell (Murphy & Weaver, 2017). Together with gp55, another precursor protein, they form a new virion next to the cell's membrane. During this assembly process the virion starts to bud from the host cell. It is immature and not yet infectious. Only after the viral protease cleaves the gp55 into its final components (capsid proteins and fusion protein), the new virus particle can infect other cells (Ghosh et al., 2016).

How exactly the virion production is activated is not yet completely understood. A promising theory, however, suggests that it depends upon the immune cell's state (active or resting), whether or not the cell's DNA polymerase II is engaged, and thus new virions are produced. Activation of the cell induces the expression of the transcription factors NFkB (Nuclear factor kappa-light-chain-enhancer of activated B cells) and NFAT (Nuclear factor of activated T-cells) which bind to the long terminal repeat segment of the proviral DNA and prompt transcription. A resting immune cell, on the other hand, does not produce new virions because the initiating signal remains absent. This suggests that the cell's state plays a role in determining if an infection is latent or active (Murphy & Weaver, 2017).
A latent infection, however, is only viable if the infected cell survives a longer period of time. If the host cell dies, the virus cannot survive. Because T cells have a longer life cycle than macrophages and dendritic cells, a virus attacking T cells is more likely to cause a latent infection. Therefore, the aforementioned tropism towards a co-factor determines not only the infected cell type, but contributes to the state of HIV infection as well (Murphy & Weaver, 2017).

These two factors, the activation-dependent production of virus particles and the viral tropism, are believed to be responsible for the clinical presentation of HIV in different phases (Murphy & Weaver, 2017), including an acute phase at the beginning, a latent or asymptomatic phase of 1-10 years, and the AIDS stage with a severely compromised immune system and the occurrence of AIDS defining diseases.

1.4. Progression of the Infection

1.4.1. Transmission

Infection with HIV can occur either through transmission of free virus particles or through transmission of infected cells. Both can be found in blood, vaginal fluids, semen and breast milk. Consequently, the paths of transmissions are sexual intercourse, contact with blood through either needle sharing or transfusion of blood products, and mother-to-child transmission through either blood, vaginal fluids, or breast milk (Murphy & Weaver, 2017). In contrast to some popular beliefs, drinking from the same glass, sharing a toilet seat, or contact with urine, saliva or even HIV+ blood with intact skin does not raise infection risk (Rockstroh, 2016). In general, the risk of transmission depends significantly on viral load in the contact body fluids, but also on the amount of fluid exchanged and on several other factors like the presence of skin lesions, co-infections with other sexually transmitted infections (STI), sexual practices and circumcision (Rockstroh, 2016). Viral load, and therefore transmission rate, usually shows two peaks. One peak occurs during the first weeks after infection, thus a person may not yet know about his or her HIV status, and the second peak occurs in the advanced state of the disease when the immune system is already compromised (Rockstroh, 2016).

Sexual intercourse is the most common mode of transmission, even though the average transmission rate through sex is rather low. Only between 0,03 and 5,60% of sexual encounters between an HIV positive and an HIV negative person result in transmission (Rockstroh, 2016). It is important to notice, however, that the risk increases significantly when dermal or mucosal integrity are compromised. Co-infections with venereal diseases cause microlesions in the skin and the mucosa which facilitate entry of virus particles (Schulz, 2009). Especially a genital infection with herpes virus could be a relevant co-factor in the spreading of HIV in high endemic regions (Mahiane et al., 2009). Some sexual practices, for example anal sex, involve a higher risk of lesions and injury, therefore increasing the transmission risk as well (Patel et al., 2014; Rockstroh, 2016). Circumcision, on the other hand, seems to be a protective factor lowering the risk of infection (Rockstroh, 2016).

Previous research has shown, that patients undergoing adequate therapy resulting in an undetectable viral load no longer carry a significant risk of transmitting and therefore protection during sexual intercourse is not absolutely necessary (Cohen et al., 2011; Rodger et al., 2016). This phenomenon is also referred to as TasP – treatment as prevention. The use of protection, for example condoms, is still recommended to protect against STIs and unintended pregnancy (World Health Organisation, 2015).

Needle sharing is a frequent source of infection in intravenous drug users. Because generally a considerable amount of blood is exchanged, the average infection rate is slightly higher than during sexual intercourse. However, initiatives like the distribution of clean needles through vending machines or doctors, as well as a variety of substitution programs can aid in reducing infection rates within the population of i.v. drug users (Rockstroh, 2016).
Transmission in a medical environment through needles contaminated with blood from an HIV positive patient rarely (0,3%) leads to infections (Rockstroh, 2016). Furthermore, risk of the virus being transferred from infected medical staff to a patient can be neglected (Center for Disease Control, 1993).

Infection during a blood transfusion has become a rarity because most countries routinely screen for HIV in all blood products, testing for antibodies as well as RNA (Murphy & Weaver, 2017). However, if a contaminated blood product is administered, transmission rate is almost 100% because of the high volume (Schulz, 2009). As a further protective measure some countries like Germany exclude people who belong to high risk populations for HIV (MSM, i.v. drug users, immigrants from high prevalence countries) from blood donations (Bundesärztekammer, 2017).

Mother-to-child transmissions can be effectively reduced to a minimum with access to modern medical care but remain a problem in countries with fewer resources. They can occur during late pregnancy through the placenta, during birth and via breast feeding with perinatal infection being the most relevant way of transmission (Murphy & Weaver, 2017). The most substantial risk factor is the mother's perinatally transferred viral load. It is highly recommended for the mother to continue or start antiretroviral treatment during pregnancy since an undetectable viral load significantly lowers the risk of transmission. This, along with an elective cesarean delivery, prophylactic antiretroviral treatment of the newborn, and refraining from breast feeding are the main preventative measures (Deutsche AIDS Gesellschaft e.V., 2017b). Because of the newborn's decreased contact with blood and vaginal fluid a cesarean section is generally regarded as safer,

but if the mother's viral load is undetectable in her blood prior to the birth, vaginal birth can be considered (Aho et al., 2018).
Regarding nursing, recommendations depend on circumstances. Due to the elevated risk of HIV transmission of breast feeding for more than 9-12 months, mothers should refrain from nursing, if a safe alternative nourishment (e.g. formula) is available (Deutsche AIDS Gesellschaft e.V., 2017b). This is true for most western countries. In some parts of the world, however, nursing can still be the safer alternative, if, for example, access to clean water or formula cannot be guaranteed (Schulz, 2009). In this case, WHO recommends breast feeding (World Health Organisation, 2018).

1.4.2. Impact on the Immune System

The virus typically enters the body through either genital or gastrointestinal mucosa. Because these membranes are regularly exposed to viruses and bacteria, they are rich in immune cells, including dendritic cells, macrophages, and effector memory CD4+ T cells. These cells express the CCR5 chemokine receptor; hence, a CCR5-tropic virus is more effective in successfully establishing an infection (Margolis & Shattock, 2006).
To penetrate the membranes, the virus seems to have developed several mechanisms. It binds to a dendritic cell residing within the membrane. Then, it is incorporated into the dendritic cell and can remain for a few days within the endosome. A particle of the virus is presented on the outside of the cell via an MHC II receptor (major histocompatibility complex II). This way the cell communicates the presence of a foreign intruder to the other immune cells. The now activated dendritic cell migrates toward a local lymph node in order to introduce the detected virus to the CD4+ T cells residing there (Murphy & Weaver, 2017). Because of the increased activity within the lymph nodes, they swell and cause lymphadenopathy (Apoola et al., 2002; Schulz, 2009).
Alternatively, the virus can bind to a DC-SIGN molecule on the outer membrane of a dendritic cell. This allows the virus to be transported to the lymph node by the cell without being incorporated. Because it resides outside the cell, it can come in contact with passing T cells and directly infect them (Schulz, 2009). In some cases, the T cells even reside within the mucosal membrane which enables direct viral entry into the T cell (Kelley et al., 2017).

Upon entry, HI virus replicates rapidly resulting in a high viral load (viremia) with over 100.000 copies/ml (Streeck & Altfeld, 2016) as well as a marked decrease in CD4+ T cells since they die as a result of viral replication. Replication takes place in macrophages and dendritic cells as well, yet they seem to be more resilient in regard to lysis than CD4+ T cells (Schulz, 2009).
This acute phase usually lasts two to six weeks. Clinical signs in patients during this time may include influenza-like symptoms in various degrees such as fever, maculopapular eczema and

lymphadenopathy (Hoenigl et al., 2016) closely resembling mononucleosis, a common misdiagnosis (Grimes et al., 2016). Yet, many patients remain asymptomatic or show very few symptoms (Robb et al., 2016) and therefore might not remember this episode later on. It has been suggested that an initially strong immune response corresponds to a more rapid progress during the course of the disease (Keet et al., 1993; Pedersen et al., 1989).

During the acute phase the body establishes an immune response with specific cytotoxic CD8+ T cells and the production of HIV specific antibodies against various viral proteins (see figure 4). It takes the body a few weeks to produce immune cells specific enough to attack the HI virus. This process is called seroconversion. Antibodies against a variety of viral proteins including gp120 and gp41 are produced, which are used for diagnostic purposes, as well as antibodies against p24, p19, and the reverse transcriptase (Schulz, 2009). Around six weeks after the initial transmission enough antibodies are produced to acquire reliable diagnostic results (Rabenau et al., 2015).

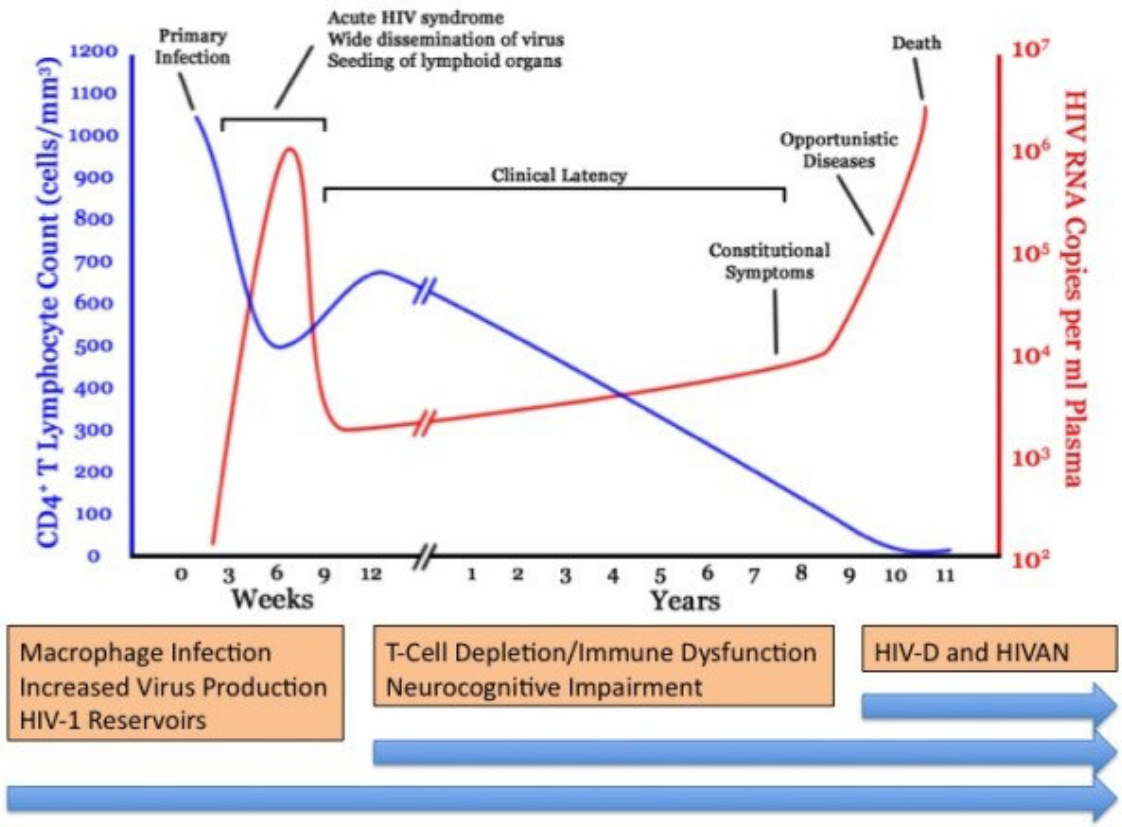

Fig. 4: **Development of CD4+ lymphocyte count and viral load over the course of an HIV infection** During the acute phase right after the transmission viral load peaks while the CD4+ T cell count decreases rapidly. As the immune system responds, the viral load begins to decrease again, reaching a low point at about 9 weeks after infection, the so-called set point. The CD4+ T cell count recovers to a certain degree. During the latent phase (marked as -//-), viral load slowly increases while the CD4+ T cell count decreases. With the onset of the AIDS stage, there is a steep increase in viral RNA, the second peak of viral load. HIV-D: HIV associated dementia, HIVAN: HIV associated nephropathy. Graph by Kogan and Rappaport (2011) used under CC by 2.0

Studies have shown that an individual's HLA (human leucocyte antigen) genes contribute to the efficacy of the CD8+ T cells. The genes determine the exact structure of the MHC II receptor responsible for the antigen presentation. The HLA type B27, for example, seems to be associated with longer survival of the individuals and a later onset of AIDS defining diseases (O'Brien et al., 2001).

The recruited CD8+ T cells decrease viral load in the blood significantly (Koup et al., 1994), at the same time the CD4+ count begins to recover. This is called viral set point and indicates the end of the acute phase. It can be used to predict disease progression. A low viral load six to twelve months after transmission is associated with a longer symptom free interval (Schulz, 2009) and better overall prognosis (Mellors et al., 1995).

Following the acute phase, the latent or asymptomatic phase begins, lasting between one and ten years. The virus is still actively replicating and destroying host cells during this time but is controlled by the body's immune system. Viral load slowly rises over a few years while the CD4+ cell count decreases correspondingly.

In about half of all patients, CXCR4 variants occur during the latent phase. This shift in tropism is usually associated with a rapid decline in health and CD4+ cell count, then rapidly entering AIDS stage (Murphy & Weaver, 2017).

1.4.3. Impact on the Central Nervous System

Generally, HI virus enters the body via mucosal membranes or directly via the blood stream. The central nervous system (CNS), however, is a separate compartment, protected by the blood-brain barrier. This barrier is semipermeable and functions bi-directionally, hence substances and cells can selectively cross the barrier from blood to the CNS (influx) and vice versa (efflux). Despite the blood-brain barrier, HIV is found within the CNS even in the early stages of infection. How the virus enters and then infects the CNS is not fully understood, but there are several theories on the entry mechanisms, as discussed below. The HI virus might enter an infected monocyte, lymphocyte or macrophage, using the immune cell like a trojan horse. Alternatively, the virus infects cells that form the blood-brain barrier such as endothelial cells or astrocytes and reaches the CNS this way. The theory of transcytosis describes a virus particle being encapsulated within a cell without the cell itself becoming infected, e.g. within an endosome or via pinocytosis. Additionally, the virus might enter through a damaged blood-brain-barrier which is now permeable for the HI virus (Arendt, 2007). The damage could result from inflammatory processes

stimulated by viral proteins such as gp120, tat, vpr and nef or through chemokines and cytokines (Arendt, 2007; Yang et al., 2009).

Once HI virus has entered the CNS, it initiates an inflammatory process. Although gp120 was found to be neurotoxic via caspase activation (Garden et al., 2002), inflammation is the more relevant mechanism which induces damage to neurons and can eventually cause neurological symptoms. The inflammatory reaction is complex and involves a multitude of substances and mediators. Tumor necrosis factor alpha (TNF-α) seems to play a key role (Wesselingh et al., 1993). Its concentration is increased in brains of HIV patients and additionally showing a genetic polymorphism of TNF-α (Quasney et al., 2001). Cell types involved in inflammatory processes are monocytes as well as macrophages and glia cells. HIV-infected monocytes seem to secrete substances that prevent cell growth and even induce apoptosis. Macrophages and glia cells produce interleukin 1 (IL-1), a pro-inflammatory cytokine, as well as nitrogen oxide (NO), the latter leading to the activation of glutamate receptors and thereby inducing neurotoxic effects (Boje & Arora, 1992).

To summarize, both, the entry and the effects of HIV on the CNS are complex and not yet entirely understood. Interactions of the virus and the immune system seem to cause inflammation which then leads to neurological symptoms in a considerable number of patients.

1.4.4. AIDS

After acute infection and an asymptomatic latency phase of variable duration, an HIV infected patient is endangered of progressing to AIDS. The time between transmission and the occurrence of AIDS varies between one and fifteen years (Schulz, 2009). This large variance is determined by the viral setpoint, the tropism of the virus, the patient's HLA type, and age (Murphy & Weaver, 2017; O'Brien et al., 2001; Rockstroh, 2016). If HIV infection is detected early and treated adequately, the latency phase can be even longer especially due to modern antiretroviral treatment. Yet, there are even nowadays so-called "late presenters" being identified as HIV-carriers for the first time when revealing full-blown AIDS symptoms (Robert Koch Institut, 2023). AIDS is defined as the occurrence of opportunistic infection (USA and Europe), or the drop of the CD4+ cell count below 200 per µl blood (USA), or both (Rockstroh, 2016). Both conditions are due to an insufficient immune response.

1.4.4.1. CDC Classification

The most common clinical classification used to define the stages of infection is the classification of the United States' Center of Disease Control (Castro et al., 1992; Schneider et al., 2008). Both

variants, the one from 1993 (table 1) and the newer version from 2008 (table 2), take the CD4+ cell count and the occurrence of AIDS-defining diseases into account. The older version also includes other diseases found in HIV patients (which are not AIDS defining), while the 2008 version is considering only the AIDS status and provides an option for patients with unknown stages.

The classification is used to document a patient's disease status; clinical improvement (e.g. increased CD4+ cell count) does not allow a switch to a better, healthier stage. This means, once a patient has gone through an AIDS defining disease, this patient will be regarded as a patient with AIDS regardless of their current health status.

Other clinical classification systems (e.g. WHO) do exist although they are not frequently used in clinical practice.

	Clinical categories		
CD4+ T cell count	**Asymptomatic, acute HIV syndrome**	**Symptomatic condition, not A or C**	**AIDS Defining Disease**
≥ 500/µl	A1	B1	C1
200-499/µl	A2	B2	C2
< 200/µl	A3	B3	C3

Table 1: **CDC Classification of 1993**
Patients are categorized according to their CD4+ cell count as well as their symptom range. Once they present with an AIDS-defining disease they are placed in category C and cannot be categorized as A or B again. µl: microliter.

Stage	**AIDS Defining Disease**	**CD4+ T cell count**
1	None	> 500/µl or ≥ 29%
2	None	200-499/µl or 14-18%
3	Documented AIDS defining disease	< 200/µl or < 14%
Unknown	No information available	No information available

Table 2: **CDC Classification of 2008**
Patients are categorized according to the CD4+ cell count and the presence of an AIDS defining disease. An additional category for patients with unknown status is available. µl: microliter.

1.4.4.2. AIDS Defining Diseases

The CDC's list of AIDS defining diseases includes mostly opportunistic infections and malignant neoplasias (see table 3). A healthy immune system is able to neutralize these pathogenic agents. In a significantly compromised immune system the opportunistic pathogen can trigger disease. The most common infections include Pneumocystis jirovecii pneumonia, esophageal candidiasis,

and infections with Mycobacterium avium–intracellulare complex while Kaposi sarcoma is the most frequent malignancy defining AIDS, followed by different types of lymphoma (Mocroft et al., 1998). In addition, wasting syndrome, lymphadenopathy, diarrhea as well as prolonged fevers are typical AIDS associated complications.

AIDS Defining Diseases
Candidiasis of the esophagus, bronchi, trachea, or lungs (but not the mouth)
Cervical cancer, invasive
Coccidioidomycosis, disseminated or extrapulmonary
Cryptococcosis, extrapulmonary
Cryptosporidiosis, chronic intestinal (≥ 1 month in duration)
Cytomegalovirus disease (other than liver, spleen, or nodes)
Cytomegalovirus retinitis (with loss of vision)
Encephalopathy, HIV related
Herpes simplex: chronic ulcer(s) (≥ 1 month in duration), or bronchitis, pneumonitis, or esophagitis
Histoplasmosis, disseminated or extrapulmonary
Isosporiasis, chronic intestinal (≥ 1 month in duration)
Kaposi sarcoma
Lymphoma, Burkitt's (or equivalent term)
Lymphoma, immunoblastic (or equivalent term)
Lymphoma, primary, of brain
Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary
Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)
Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
Pneumocystis jirovecci pneumonia
Pneumonia, recurrent
Progressive multifocal leukoencephalopathy (PML)
Salmonella septicemia, recurrent
Toxoplasmosis of the brain
Wasting syndrome due to HIV

Table 3: **List of AIDS Defining Diseases** according to the CDC (MMWR, 1992)

1.4.4.3. Co-Infections and Co-Morbidities

Aside from the aforementioned AIDS-defining diseases HIV patients can acquire various co-infections and co-morbidities.

Due to similar ways of transmission and a high prevalence within risk groups, sexually transmitted diseases such as hepatitis B (HBV) and hepatitis C (HCV) are common co-infections. Pre-existing STIs like syphilis, gonorrhea, chlamydia and condylomata accuminata even increase the risk of HIV transmission, as mentioned above.

About 6-14% of HIV patients suffer from chronic hepatitis B (Alter, 2006). HIV leads to faster progression of hepatitis, a higher risk of cirrhosis and an overall increased mortality (Wasmuth et

al., 2016). In patients with a history of acute hepatitis B, reactivations have been observed due to the HIV-associated immunosuppression (Shouval & Shibolet, 2013). Co-infection with hepatitis C is found in 15% of all HIV patients, especially in intravenous drug users. HIV increases progression of hepatitis C, although it remains unclear if HCV negatively influences the HIV infection vice versa (Rockstroh et al., 2005).

In addition to co-infections, there is an elevated risk for developing carcinomas in HIV-positive patients (Franceschi et al., 2010). This risk directly correlates with the immune status: A lower CD4+ cell count is associated with a higher risk for malignant tumors and vice versa (Monforte et al., 2008; Reekie et al., 2010). Examples for HIV associated carcinomas are seminoma, bronchial carcinoma, and anal carcinomas, with the latter being the most common AIDS associated malignancy that is not classified as AIDS-defining.

Moreover, HI virus can afflict the peripheral and central nervous system in various ways. Polyneuropathy, for example, affects many HIV patients, e.g. HIV-1 associated sensitive polyneuropathy, Guillain-Barré-Syndrome, especially in the acute phase, or toxic, medication-induced polyneuropathy.

Psychiatric comorbidities such as affective disorders, alcohol and substance abuse, and bipolar or schizophrenic psychotic episodes can occur as primary disease or as a result of living with HIV. The diagnosis, especially of depressive episodes, can be difficult since common symptoms, e.g. weight loss and cognitive impairment, can overlap with those of HIV-1 associated neurocognitive disorder (HAND) or systemic HIV-disease (Arendt, 2007). HAND will be discussed in greater detail in the next paragraph.

1.4.5. HIV-1 Associated Neurocognitive Disorder

Navia et al. discovered as early as 1986 that HIV can affect patients´ cognitive and motor functions as well as induce behavioral abnormalities (Navia, Cho, et al., 1986; Navia, Jordan, et al., 1986). This symptom complex was since then categorized as HIV-1 associated encephalopathy and AIDS-dementia complex and is nowadays referred to as HIV-1 associated neurocognitive disorder or HAND. While most HIV associated symptoms and diseases have decreased since the beginning of the cART (combined antiretroviral therapy) era in 1996 the incidence of HAND has increased. This increase refers to the milder forms of asymptomatic and mild impairment, though there are less cases of the more severe form, dementia (Heaton et al., 2011). Nevertheless, HAND does affect these patient's daily life and is furthermore associated with a shortened lifespan (Sevigny et al., 2007). Between 25-50% of all HIV positive patients seem to develop a form of HAND during their lifetime (Heaton et al., 2011; Sacktor et al., 2016).

To affect the central nervous system the virus first must enter this compartment. The exact pathomechanism is not entirely understood yet, as discussed earlier (Eggers et al., 2017). It is hypothesized, that infected monocytes and lymphocytes cross the blood-brain-barrier without being identified as infected by the local immune cells. The virus, hidden in the carrier cells, then infects immune cells within the brain tissue and cerebrospinal fluid (CSF).
This appears to ensue during the primary infection. While the patient initially remains asymptomatic, an inflammatory response (pleocytosis) can already be detected within the cerebrospinal fluid at this stage (Marra et al., 2007). After replication, viral particles can be detected in the CSF. Distinct virological analysis has shown that diverse mutations which are different from those found in plasma of an individual patient can occur (Arendt, 2007; Garcìa et al., 1999). With distinct virus strains existing within the same patient, the issue of resistances against retroviral substances arises as well. Concentration of HIV-RNA in cerebrospinal fluid appears to correlate with the onset of neurological symptoms (Christo et al., 2005). Several studies in animals and humans have shown that an early intervention with cART including drugs that reach the CNS is associated with a better neurological outcome (Marcondes et al., 2009; Tozzi et al., 2007).

Not every patient develops HAND. If and when the CNS-infection provokes symptoms is not yet clear but genetic factors relating to the immune system are discussed as a contributing factor (Olivier et al., 2018). The underlying causes for a symptomatic HIV associated neurocognitive disorder seem to be not the virus itself but the inflammatory reaction that is triggered by the presence of HIV within the CNS (Arendt, 2007).
The current nomenclature follows the revised classification by Antinori (Antinori et al., 2007). The classification, as depicted in table 4, includes objectively tested and subjective deficits in the following categories: memory, attention, executive function, working memory, verbal skills, speed of information processing, sensory and perceptual function, and motor skills.

While patients with asymptomatic neurocognitive impairment (ANI) remain clinically asymptomatic, patients with mild neurocognitive disorder (MND) experience mild symptoms and patients with HIV-1 associated dementia (HAD) show severe impairment in their daily activities. It might be helpful to interview relatives and close friends to more adequately assess a patients subjective impairment (Arendt, 2007).

HIV-1-associated asymptomatic neurocognitive impairment (ANI)	Acquired impairment in cognitive functioning (NCI), involving at least two ability domains, documented by performance of at least 1 SD below the mean[a] on standardized neuropsychological tests[b] The cognitive impairment does not interfere with everyday functioning (e.g., mental acuity, inefficiency in work, homemaking, or social functioning)
HIV-1-associated mild neurocognitive disorder (MND)	Neuropsychological test results as with ANI At least mild interference in daily functioning (self-report or witnessed by knowledgeable others)
HIV-1-associated dementia (HAD)	Neuropsychological test results as with ANI, but performance in cognitive testing impaired by at least 2 SD of the mean Marked interference with day-to-day functioning

Table 4: **International terminology of HIV-associated neurocognitive disorders (HAND)** according to Eggers et al. (2017) and Antinori et al. (2007).
SD: Standard deviation
a Adjusted for age-education-appropriate norms
b The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/ executive; memory (learning; recall); speed of information processing; sensory-perceptual, motor skills

Diagnosis of HAND requires clinical assessment and neuropsychological testing. There are several tools available to screen for HAND, for example the HIV dementia scale by Power (Power et al., 1995) and the International HIV Dementia Scale by Sacktor (Sacktor et al., 2005). However, application of more extensive test batteries for the above mentioned neurocognitive and motor functions should be used (Eggers et al., 2017).

Motor function seems to be an early predictor of neurocognitive performance in HIV patients and of the overall outcome and mortality in HIV patients (Naveed et al., 2021).

Additional diagnostics such as a psychiatric evaluation, imaging and CSF analysis are performed to exclude important differential diagnoses, these include depression or a history of alcohol and substance abuse as well as traumatic brain injury or disability. Furthermore, a co-infection with hepatitis C or opportunistic infections like cytomegalovirus encephalitis, cerebral toxoplasmosis, progressive multifocal leukoencephalopathy (PML), as well as metabolic diseases are important differential diagnoses (Arendt, 2007). Of course, alternative types of dementia need to be considered as well. Especially the distinction between HAND and vascular dementia seems to be in need of further clarification because of significant overlap (Cysique & Brew, 2019). Finally, it

should be taken into account that cART itself can have toxic effects that might lead to neurocognitive deficits (Arendt, 2007).

If HAND is diagnosed in a patient who does not yet receive cART, treatment should begin immediately. Since the virus has infected cells in the central nervous system it is of utmost importance that the chosen medication is able to penetrate the blood-brain-barrier. For an effectiveness evaluation of CNS-penetrating substances see Letendre (2016; 2008) and the classification of substances according to their CPE Score (CNS Penetration Effectiveness). For patients already on cART treatment regimen should be adapted.

1.5. Diagnosis and Treatment

1.5.1. Diagnosis

Once infected with HI virus, the body starts an immune response, including the production of antibodies. Producing antibodies takes up to six weeks. Antibodies against the virus proteins p24 (capsid) and gp120 and gp41 (membrane) respectively, can be detected to confirm infection with HIV (Schulz, 2009).

Diagnostic procedure is divided into several steps. First, a screening using ELISA (enzyme-linked immunosorbent assay) is applied. It is recommended to test for both, HIV-1 and HIV-2 as well as for freely circulating p24 (Rabenau et al., 2015). The test criteria reach over 99% for both, sensitivity and specificity (Schulz, 2009). Therefore, a negative test result can eliminate a possible HIV infection with very high reliability. There is, however, the issue of the “detection window”. Within the first six weeks of infection, the body has not yet produced the antibodies needed for a positive ELISA result. If exposure to the virus was less than six weeks ago, using NAT (nucleic acid test) instead is recommended (Rabenau et al., 2015).

A positive or unclear result in the screening ELISA always demands additional testing, using either western blot or NAT; both are equally sensitive. In either case, the chosen method should be capable of differentiating between HIV-1 and HIV-2 (Rabenau et al., 2015).

Should results be negative in the confirmation test, the screening result is classified as false positive. In case of remaining clinical suspicion or unclear results, retesting after one to three weeks is recommended. If result of the NAT or western blot is positive, a second blood sample drawn from the same patient should be tested to confirm diagnosis and to rule out a mix-up of patient samples (Rabenau et al., 2015).

In addition, PCR (polymerase chain reaction) can be used to detect viral RNA. While PCR can detect either viral RNA in serum or proviral DNA in cells, the analysis of the freely circulating RNA

is more sensitive. Nowadays, real time PCR is used, which can quantify the viral load (Schulz, 2009).
PCR can be used to confirm diagnosis, especially in very early stages, or to test blood products. Viral load is usually measured to monitor treatment (Schulz, 2009).

1.5.2. Goals and Start of Treatment

HIV remains an incurable, chronic disease, with the exception of rare, complex cases in which the virus seemed to have been eliminated after a bone marrow transplantation (Gupta et al., 2021). The virus can persist within different reservoirs (CNS, lymphatic system) even under treatment (Chun et al., 2005). However, the available treatment options have improved considerably and with life-long successful treatment a nearly normal life expectancy is a reality for HIV patients today (Marcus et al., 2016; Wandeler et al., 2016). In clinical terms, the treatment aim is prolongation of life and the improvement of quality of life for each patient. Treatment aim in medical terms is viral load below the level of detection and normalization of the CD4+ cell count (Hoffmann, 2016).
Within the last years, guidelines of the US as well as of Germany and Austria have been updated to recommend treatment start as soon as possible after HIV diagnosis.
Several high-profile studies, for example SMART 2006 and START 2015, have shown that every patient benefits from early and continuous treatment, regardless of the CD4+ cell count (SMART, 2006; START, 2015). The German AIDS Society (DAIG) differentiates between mandatory therapy start for symptomatic patients, patients with hepatitis or pregnant patients, and patients with a CD4+ cell count below 500/µl and a recommended therapy start for asymptomatic patients with a CD4+ cell count above 500/µl.

1.5.2.1. Treatment Success and Failure

Three factors are relevant to quantify the body's response to treatment: the virological response (viral load), the immunological response (CD4+ cell count) and the clinical response (absence of diseases) (Hoffmann, 2016).
Approximately three to four months after starting treatment, viral load should be below the level of detection (in blood). Viral load of more than 50 copies per ml blood signifies treatment failure (Deutsche AIDS Gesellschaft e.V., 2017a). If the virus remains detectable after six months, treatment failure is likely. The development of viral load right at the beginning of treatment can predict further progression. An immediate drop within the first weeks is associated with better therapy results (Powderly et al., 1999) while a slower decrease is often associated with treatment

failure later on (Grant et al., 2013). Haubrich et al. (2011) even defined the seven-day mark to be predictive for treatment failure. A so-called “blip”, however, defined as a small increase in viral load of 50-200 copies/ml for short periods of time, is not associated with clinical symptoms, resistance development or drops in CD4+ cell count and occurs most likely due to measurement inaccuracies and statistical variations (Nettles et al., 2005).

In general, treatment failure prevalence shows a decreasing trend (Lampe et al., 2006). This can be explained by fewer cases with resistant viruses because of improved therapy options and an earlier therapy start. In case of total treatment failure (all available options affected), consensus is to continue treatment nonetheless, since cART seems to lower mortality independent of viral load (Mocroft et al., 2012).

Immunological response occurs slightly later than virological response. The CD4+ cell count responds to treatment with a marked increase followed by a plateau phase with a continuous but slow rise (Mocroft et al., 2007). The cell count may never fully recover (it remains <500 cells/µl) (Kaufmann et al., 2003), yet once a threshold of more than 300 cells/µl is reached, the cell count seldomly drops below 200, presumed the viral load remains suppressed (Gale et al., 2013).

A discordant response is a possibility as well. In some patients, viral load and cell count do not correspond, i.e. a low viral load occurs with a low cell count and vice versa (Moore et al., 2005; Tan et al., 2008). This is associated with a higher mortality (Engsig et al., 2014). Possible reasons are patient age, autoimmune diseases and negative interactions between antiretroviral medications (Hoffmann, 2016).

In summary, to evaluate whether a treatment regimen is successful or failing is a complex task requiring regular observation of a patient’s symptoms and lab results. Achieving a better course of treatment for the individual patient can be challenging, since many independent variables play into the immune system’s response.

1.5.3. Classes of Drugs

Since the discovery of HIV in the early 1980s and the development of the first antiretroviral drug in 1987 (Brook, 1987), treatment options have improved considerably. It is recommended to use a combination of substances from the following classes of drugs:

- Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs/NtRTIs)
- Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)
- Protease Inhibitors (PIs)
- Entry Inhibitors
- Integrase Inhibitors (INIs)

These drugs attack four different viral replication steps. Because of the virus' tendency to mutate and develop resistance mechanisms, this diversity is of uttermost importance. First, if resistance occurs, a switch to another class might be an option. Second, and more important, targeting multiple sites at once has proven to prevent selective mutations and allows for longer therapy success. Therefore, combination of multiple antiretroviral substances remains the key point of modern antiretroviral therapy.

Within each class there are several substances currently in use. Therapy regimen always consist of a combination of three or more drugs of different classes, according to the individual patient's needs, resistance situation, side effects and lifestyle. A patient's successful therapy regimen does not necessarily need changing, even if it consists of older drugs (Deutsche AIDS Gesellschaft e.V., 2017a).

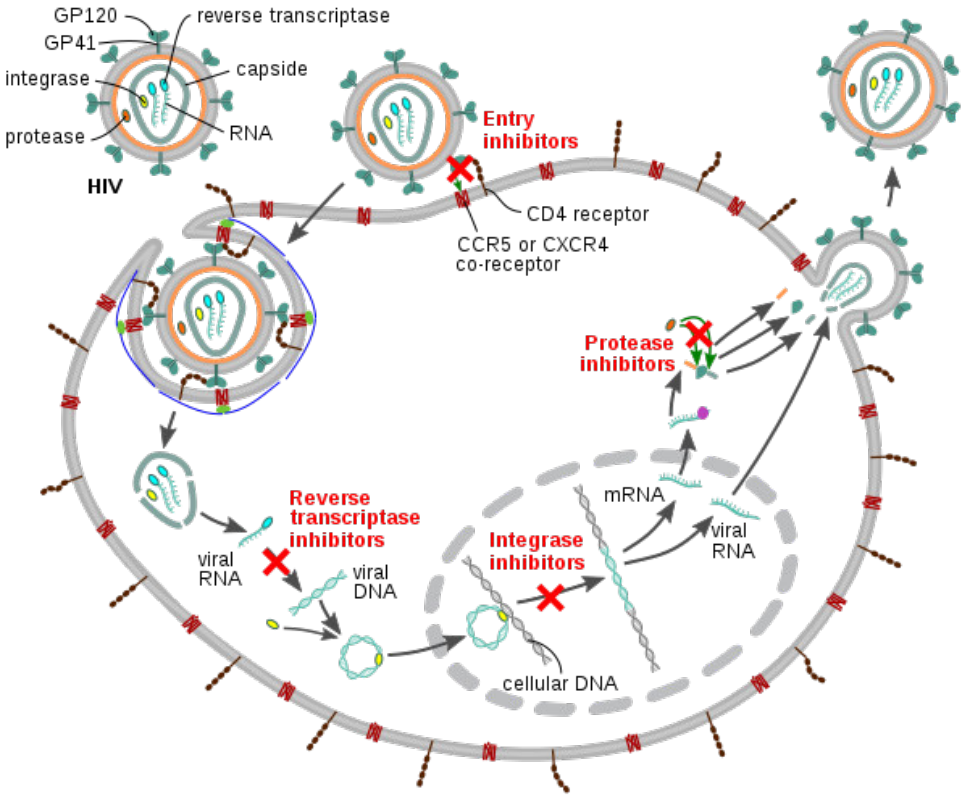

Fig 5: **Target sites of antiretroviral drugs within the replication cycle of the HI virus**
Antiretroviral drugs can inhibit the entry of the virus into the cell, while NRTIs and NNRTIs interfere with the viral reverse transcriptase thus preventing transcription. Integrase inhibitors prevent the merging of viral and human DNA and protease inhibitors prevent the correct assembly, resulting in non-infective viral particles. Graphic by Thomas Splettstoesser used under CC BY 3.0 license.

1.5.3.1. NRTIs and NtRTIs

Nucleoside or Nucleotide Reverse Transcriptase Inhibitors are modified substrates of the reverse transcriptase, competing with the cell's nucleosides adenosine, cytidine, thymine, and guanine. The NRTIs are prodrugs and need to be activated once inside the host cell by adding three phosphates. They have a modified sugar molecule which is missing the 3' hydroxyl group (Holec et al., 2017). If the analogs are used to build the DNA strand transcription stops. Because of the missing 3' hydroxyl group, the viral reverse transcriptase cannot form the phosphodiester bind for chain elongation. Hence, the replication process terminates (Cihlar & Ray, 2010).

NRTIs were the first antiretroviral drug to be developed. In 1987, Zidovudine (AZT) was introduced to the market but although it was sensational at that time, it is not used regularly nowadays because of its side effects (Deutsche AIDS Gesellschaft e.V., 2017a). Due to its high CNS penetration capacity, it might still be used in patients with HAND (Hoffmann, 2018) but other NRTIs have taken its place as backbone of cART.

Most recommended regimen contain two different NRTIs plus one substance from another class. The most common NRTI backbone combinations are Abacavir (ABC) and Lamivudin (3TC) and Tenofovir-Alafenamid (TAF) with Emtricitabine (FTC) (Deutsche AIDS Gesellschaft e.V., 2017a)**.** Although NRTIs are widely used, they have their problems. Side effects include lipodystrophy, fatigue, headache, lactate acidosis, polyneuropathy and mitochondrial toxicity (Brinkman et al., 1999; Dieterich, 2003). An inhibition of the telomerase resulting in cell ageing is being discussed with inconclusive findings (Leeansyah et al., 2013; Solomon et al., 2014), as well as a possibly increased myocardial infarction risk for Abacavir (Llibre & Hill, 2016; Sabin et al., 2016). Abacavir is also associated with hypersensitivity reactions. Since the association of these reactions with HLA B57 gene has become clear and testing for the gene is mandatory prior to treatment with Abacavir (Mallal et al., 2008), this complication has become neglectable. In general, all NRTIs can be subject to resistance development and combination with other classes is mandatory.

1.5.3.2. NNRTIs

Non-Nucleoside Reverse Transcriptase Inhibitors target the reverse transcriptase directly. They bind non-competitively to the enzyme close to the substrate binding site, inducing a conformation change of the enzyme. This reduces speed and efficiency of polymerization and therefore negatively interacts with viral replication (de Béthune, 2010; Sluis-Cremer & Tachedjian, 2008). NNRTIs are not prodrugs but are metabolized by the cytochrome p450 system and therefore prone to interactions (Usach et al., 2013). They induce mutations in the reverse transcriptase very rapidly, sometimes even after a single dose (Eshleman et al., 2004; Giaquinto et al., 2006), resulting in decreased susceptibility rates in approximately 5% of patients in Europe. Therefore,

testing for resistance prior to prescription of NNRTIs is necessary (Hofstra et al., 2016). If virological failure occurs during treatment, the use of NNRTIs should be terminated to avoid further resistance development. The only substance actually recommended in Germany is Rilpivirin (Deutsche AIDS Gesellschaft e.V., 2017a). Despite the disadvantages, it should be considered as maintenance therapy especially in patients with low viral load and resistances to PIs or INIs.

1.5.3.3. Protease Inhibitors

Towards the end of the replication cycle, protease slices the gag-pol proteins within newly produced viral particles and therefore turns immature, non-infective viral particles into infectious viruses. Protease inhibitors (PI) block the enzyme which results in a decrease of infectious viruses (De Clercq, 2013). They are less susceptible to resistance development than integrase inhibitors and NNRTIs and applicable to patients with high viral loads or low adherence to their therapy regimen (Hoffmann, 2018). At the moment, there are several substances in use, yet only Darunavir/r and Atazanavir/r are recommended (Deutsche AIDS Gesellschaft e.V., 2017a). Except for Atazanavir they all need boosting, indicated by the /r or /c, which means they are prescribed in combination with a second substance, either Ritonavir (r) or Cobicistat (c), to stabilize and uphold steady plasma levels (Ghosh et al., 2016). Ritonavir is a strong inhibitor of the cytochrome p450 system and allows for raise in maximum concentration, lower drug doses and longer half-life of the medication (Kempf et al., 1997). Since boosting affects the cytochrome p450 system, interactions with various co-medications are likely and need to be considered. Additionally, the higher maximum concentration might lead to more side effects. These can include lipodystrophy, dyslipidemia (Nolan, 2003), sexual dysfunction (Schrooten et al., 2001), platelet activation (Laurence et al., 2018), and cardiovascular disease (Lundgren et al., 2018; Nolan, 2003). If side effects occur, plasma levels of the protease inhibitors should be monitored.

1.5.3.4. Integrase Inhibitors

During the replication cycle integrase initiates merging of viral DNA strand with the host cell's DNA. The newly synthesized DNA is processed at both 3' ends by the viral integrase and then transported into the core. Inside the nucleus, the viral integrase incorporates the virus DNA into the cell's DNA through strand transfer (Hare et al., 2010).
Integrase inhibitors (INI) prevent binding of the 3' hydroxyl groups to the host DNA. There are four substances available on the market: Raltegravir since 2007, followed by Elvitegravir (needs to be boosted) (Hoffmann, 2018), Dolutegravir and Bictegravir. They now represent a substantial

component of cART. However, since integrase inhibitors are a rather new class of drugs, there are still some difficulties and questions. They seem to be susceptible to resistances (Anstett et al., 2017), the measuring of plasma concentration is not reliable and precise enough to efficiently be used for monitoring (Cattaneo et al., 2012) and possible long-term effects are yet unknown. Side-effects appear to include mild neuropsychological effects such as sleep disturbances and depression and are associated with weight gain (Menard et al., 2017; Penafiel et al., 2017), all are proven to correlate with INIs. In general, integrase inhibitors are a highly promising class of antiretroviral drugs. With Dolutegravir plus Rilpivirin, the first drug combination without an NRTI backbone has entered the market in 2018, improving options for treatment simplification (Capetti et al., 2018).

1.5.3.5. Entry Inhibitors

Entry inhibitors can be divided into three subgroups according to their target. Attachment inhibitors prevent attachment of the viral proteins gp120 and gp41 to the cell's surface, co-receptor antagonists prevent the virus from binding to co-receptors CCR5 or CXCR4, and fusion inhibitors attack gp41 during its conformational change, necessary for initiating the fusion between virus and host cell (Mostashari Rad et al., 2018).

While attachment inhibitors are still in the clinical testing phase, co-receptor antagonist Maraviroc is available since 2007 with FDA (Food and Drug Administration) admission in the US (Center for Drug Evaluation and Research, 2007) and restricted admission in Europe (Kuritzkes et al., 2008). It targets the CCR5 co-receptor, prevents the ligand from binding to CCR5, and effectively inhibits downstream signaling (Woollard & Kanmogne, 2015). The CCR5 co-receptor tropism is more relevant for viral replication in early stages of the infection, since a switch in tropism towards CXCR4 co-receptor occurs in most patients at later stages. Testing for viral tropism is mandatory before beginning treatment with a co-receptor antagonist. With this limitation, Maraviroc has been shown to effectively decrease viral load, even in pretreated patients (Genebat et al., 2010).

T-20 is the only available fusion inhibitor and is rarely used. It needs to be applied subcutaneously, causes skin reactions and is very expensive, so alternative substances are recommended (Hoffmann, 2018).

While fusion inhibitors are almost out of use, other new substances such as an antibody against a viral surface structure (Gardner & Farzan, 2017) and a new attachment inhibitor look promising (Lataillade et al., 2018).

1.5.4. Therapy and Resistance Management

Prior to the start of a new antiretroviral therapy regimen, testing for existing resistances is highly recommended. Resistances are present in around 11% of therapy naïve patients in Germany (Hauser et al., 2017). Since certain resistance mutations are associated with further mutations or resistances, these should be kept in mind and might require repetitive testing (Alteri et al., 2011). The overall treatment efficacy is reduced significantly, should the patient be treated with one or more substances for which "their" HI-virus variant has developed a resistance. Therefore, a combination of three fully effective substances should be selected (Little et al., 2002; Wittkop et al., 2011).

The initial therapy regimen or the basic therapy regimen consists of a backbone of two NRTI plus either an NNRTI, a boosted PI or an INI (Deutsche AIDS Gesellschaft e.V., 2017a). A therapy combination with less than three components or a combination of three NRTIs has been found to be inferior to the above-mentioned options and is not recommended at the start of therapy (Gulick et al., 2004).

While the Panel on Antiretroviral Guidelines for Adults and Adolescents in the US favors Bictegravir with TAF and FTC (2018), the recommended backbones according to the DAIG are ABC and 3TC or TAF and FTC (Deutsche AIDS Gesellschaft e.V., 2017a). TDF/FTC or TDF/3TC are considered alternative options. Rilpivirin is the only recommended NNRTI and should be administered to patients with an initial viral load of less than 100.000 copies/ml and in combination with TAF/FTC, alternatively in combination with ABC/3TC. Protease inhibitors are exclusively available as fixed combination with a booster, either Ritonavir or Cobicistat (Hoffmann, 2018). Darunavir is recommended to be added to ABC/3TC or TAF/FTC while Atazanavir with either backbone might be considered as an alternative. Other PIs are not recommended for first line therapy. Recommended integrase inhibitors are Dolutegravir, Bictegravir and Raltegravir, while Elvitegravir is recommended for the combination with TAF/FTC only. For an overview of recommended combinations by the DAIG see table 5.

Additional combinations featuring different or more than three substances are, of course, possible and might be considered for the individual patient but are not part of the recommendations for first line therapy.

Should resistance develop and, consequently, the chosen therapy regimen fail to suppress viral load in blood, a switch might be necessary. In this case, genotyping is recommended. Also, differential diagnoses of virological failure are low plasma levels, low adherence, interactions with co-medication, or new co-morbidities such as lymphoma. For patients who do not respond adequately to initial therapy regimen, other substances from all classes might be considered.

Additional reasons to consider a treatment change are pregnancy, co-infections, side effects or patient request (e.g. a simpler therapy regimen) (Deutsche AIDS Gesellschaft e.V., 2017a).

Backbone		Combination Drug
NRTI combinations – recommended • TAF/FTC • ABC/3TC NRTI combinations – alternative • TDF/FTC • TDF/3TC	combined with	**INI** – recommended • Dolutegravir • Bictegravir • Raltegravir • Elvitegravir/c (+TAF/FTC) **NNRTI** – recommended • Rilpivirin (+TAF/FTC) **PI** – recommended • Darunavir/r or Darunavir/c **PI** – alternative • Atazanavir/r or Atazanavir/c

Table 5: **Antiretroviral drug combinations for first line therapy as recommended by the DAIG**
Combination antiretroviral therapy consists of two NRTI in combination with a drug from another class as seen on the right. Prior to therapy start resistance testing is always recommended.
NRTI: nucleoside/nucleotide reverse transcriptase inhibitor
INI: integrase inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor, PI: protease inhibitor
TAF: Tenofovir-Alafenamid, FTC: Emtricitabin, ABC: Abacavir, 3TC: Lamivudin, TDF: Tenofovir-Disoproxil
/c: boosted with Cobicistat, /r: boosted with Ritonavir

1.5.5. Adverse effects and Interactions

As every medication, antiretroviral drugs have adverse effects as well as interactions with other medications. Usually, family care or primary care physicians monitor such side effects including a complete blood sample analysis, metabolic and lipid profiles as well as urine analysis (Reust, 2011). Common side effects depend on the substance class.

While the side effects mentioned in table 6 are the direct effects of cART, there are also secondary long-term effects. It is well established that hypercholesterinemia and hypertriglyceridemia are highly relevant risk factors for cardiovascular and cerebrovascular diseases, including myocardial infarction and stroke. While AIDS was the leading causes of death among HIV positive patients in the early years of the HIV pandemic, antiretroviral treatment has changed mortality statistics. Today, cardiovascular and cerebrovascular diseases, followed by hepatic diseases, are among the leading causes of death in HIV positive patients, partly due to the adverse effects of treatment (Chen & Dugas, 2019; Croxford et al., 2017). Therefore, considering and monitoring adverse effects of antiretroviral medication should be a major part of HIV-care.

Drug Class	Adverse Effects
NRTI	lactic acidosis, lipodystrophy, bone marrow depression, renal insufficiency, decrease in bone mineral density
NNRTI	rash (Steven-Johnson Syndrome), neuropsychiatric effects, headaches, insomnia, suicidal ideation, neurotoxicity, QT time prolongation
PI	lipid disorders including hypercholesterinemia and triglyceridemia, hepatotoxicity, hyperbilirubinemia, cholelithiasis, nephrolithiasis, lipohypertrophy, glucose intolerance, higher cardiovascular risk, gastrointestinal symptoms
Entry and Fusion Inhibitors	neutropenia, increased risk of pneumonia, injection side reactions
Integrase Inhibitors	myopathy, rhabdomyolysis, hepatotoxicity, hypersensitivity, depression, weight gain, hypercholesterinemia, triglyceridemia, insomnia

Table 6: **Common adverse effects of antiretroviral drug classes**
Adapted and summarized from Panel on Antiretroviral Guidelines for Adults and Adolescents from 2018 and 2024 (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2018, 2024).
NRTI = Nucleoside reverse-transcriptase inhibitor, NNRTI = Non-nucleoside reverse-transcriptase inhibitor, PI = Protease inhibitor,

Interactions of cART with other medications are mainly due to metabolization by the cytochrome P450 system. This is true for NNRTIs and PIs as well as the newer substance Maraviroc. The most common interactions occur with antibiotics such as rifampine and marcolides, anticonvulsants (carbamazepine, phenytoin, phenobarbital), some calcium channel blockers and antagonists such as diltiazem, proton pump inhibitors as the very commonly prescribed pantoprazole, and certain benzodiazepines including lorazepam and oxazepam (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2020; Reust, 2011). While interactions need to be considered before every new drug prescription, benefits of cART outweigh negative effects and suitable therapeutic combinations can be found for the vast majority of HIV patients.

1.5.6. Prevention

According to the WHO effective prevention of new HIV infections has failed so far. The recommended use of condoms and behavioral approaches (e.g. abstinence) seem to be insufficient. While an HIV positive person receiving treatment that is effectively suppressing viral load, is not infectious (Therapy as Prevention, TasP), about 30% of new infections result from relations with seroconverters, recently infected persons who do not yet know about their HIV status (Chibo et al., 2012). This makes prevention efforts even more difficult. The relatively new

approach of biochemical methods of prevention might improve the situation and help in reducing the number of newly infected individuals in the future.

1.5.6.1. Post-Exposure Prophylaxis (PEP)

PEP with Zidovudine is recommended since 1989 following relevant HIV exposure in a professional context, especially for medical staff (Henderson & Gerberding, 1989). Today's guidelines recommend PEP for every person experiencing an exposure which bears a significant risk of infection, including sexual intercourse, blood transfusions, and i.v. drug usage (Deutsche AIDS Gesellschaft e.V., 2018b).

Prophylaxis should begin as soon as possible after exposure, ideally within 24 hours, but no later than 72 hours. In addition to the chemical prophylaxis, every patient should be tested for HIV antibodies, and given an apparent risk, for infection with HBV and HCV. While the concept of PEP seems practical and useful, people seem reluctant to take advantage. This may be due to lack of knowledge, inaccessibility, stigma or discouraging experiences with health care workers distributing PEP in the past (Palich et al., 2017). A study found, however, that sex workers who have used PEP in the past, recommend it and would consider using it again in the future (Restar et al., 2017).

1.5.6.2. Pre-exposure Prophylaxis (PrEP)

PrEP on the other hand is a continuous chemoprophylaxis taken by HIV negative persons who are at risk of exposure. The only combination recommended at the moment is Tenofovir plus Emtricitabine, although additional substances and methods of application are likely to be recommended in the future (Krakower et al., 2015). PrEP is recommended for MSM with risk-behavior such as unprotected anal sex, and for serodiscordant couples, where the HIV positive partner shows viremia >200 copies/ml due to insufficient cART, no cART or within the first weeks of cART. Persons at risk like i.v. drug users without access to sterile needles are eligible as well (Deutsche AIDS Gesellschaft e.V., 2018a). Since 2014, the WHO additionally recommends PrEP to transgender persons, sex workers and imprisoned persons (World Health Organisation, 2014), though the DAIG does not follow these recommendations since the HIV prevalence in Germany is comparatively low (see statistic section above).

When taken regularly, PrEP results in a risk reduction of up to 86-99% (Anderson et al., 2012; McCormack et al., 2016), although lower adherence leads to lower effectiveness (Fonner et al., 2016).

The IPERGAY study showed an effective protection for on demand use as well (Molina et al.,

2017) though only for male participants. The concentration within the female genital tract seems to rise slower and decrease faster, rendering the on-demand usage unadvisable (Cottrell et al., 2016). The periodic use of PrEP is described as off-label use by the DAIG.
Problems with PrEP seem to be the increase in risky sexual practices and the elevated risk of STIs due to unprotected sex (Newcomb et al., 2018; Nguyen et al., 2018), so PrEP might not be the solution to decrease HIV incidence on a global level after all despite its advantages for the individual.

1.5.6.3. Vaccination

A vaccination is not yet available despite ongoing efforts since the 1980s. The high mutation rate and therefore the immense diversity of HI virus variants complicate the task. Nonetheless, the scientific community is more optimistic than ever (Kresge, 2018). Significant breakthroughs have been obtained using antibodies in experiments with mice, and scientists hope to develop an effective vaccine based on these findings (Escolano et al., 2017). Jones et al. (2020) published a summary of the efforts and recent developments. The development of mRNA vaccines due to the recent SarsCov-2 pandemic has proven that these new types of vaccines are a valid alternative, thereby opening new possibilities for an HIV vaccine.

1.6. Heavily Treated Patients

Heavily Treated Patients (HTP), the focus group of this doctoral thesis, are defined as HIV positive patients who receive a minimum of five different antiretroviral substances in order to control their HIV infection.
This differentiates them from the majority of HIV patients who receive the standard first line therapy regimen of a backbone therapy with two drugs plus one additional substance, a total of three antiretroviral substances.
Heavily treated patients are a minority within the HIV positive population and therefore not much scientific data regarding this subpopulation is available.

1.6.1. Resistance and Intensified Therapy Regimen

While many HIV positive patients receiving cART reach undetectable viral loads and survive in good health, some are less successful and develop resistances against one or more antiretroviral

medications. These resistances are based on viral mutations which can occur in therapy-naïve patients as well as in those who are treatment experienced.

Among transmitted resistances those against NRTIs are most common, followed by those against NNRTI and PIs (Hofstra et al., 2016)**.** The International AIDS Society provides a regularly updated list with drug-resistance mutations, linked to the responsible mutation (Wensing et al., 2017). Documented drug resistance in an HIV patient is a distinct predictor of virological failure. In their study, Lepri et al. (2000) found resistance to one or more drugs in 76% of all patients with virological failure indicated by the increase in circulating HIV RNA copies. This is associated with higher morbidity and a faster disease progression (Katzenstein et al., 1996; Zaccarelli et al., 2005). Therefore, the recommended target is a viral load of less than 50 copies per ml blood, for treatment-naïve and for treatment-experienced patients alike (Hammer et al., 2006; Zaccarelli et al., 2009). To achieve this target for patients with multidrug resistance, additional measures might be necessary.

A patient-centered approach with unusual combinations of cART is a promising option (Taramasso et al., 2015). The DAIG explicitly notes in their guidelines that divergent antiretroviral combinations are allowed, as long as they are of proven benefit to the individual patient (Deutsche AIDS Gesellschaft e.V., 2017a). Raising the number of substances included in a regimen is an additional option. These “heavily treated patients” (HTP) receive a combination of an optimized backbone regimen with two additional substances which can help to achieve an undetectable viral load even in patients with resistances (van Lunzen, 2007). To determine the optimized backbone regimen consisting of two NRTI plus either a PI, INI or NNRTI, prior resistance testing is crucial. While genotyping has become the standard (Deutsche AIDS Gesellschaft e.V., 2017a), phenotypic testing seems to provide additional benefit with a higher rate of treatment success, especially in the case of multi-drug-resistant virus strains (Fehr et al., 2011). As an alternative - albeit still experimental - strategy, reduced viral fitness which in some cases results from viral mutations, can be used to achieve an improved clinical outcome for these patients (De Luca, 2006).

1.6.2. Demographics

While age or duration of infection are not classified as stand-alone risk factors to develop multi-drug resistance, there is evidence that the risk for resistance increases over time. Patients who received treatment regimens following former guidelines, including first generation drugs and monotherapy are at higher risk of developing resistant viral strains (Napravnik et al., 2007). However, individual patient factors leading to incompliance seem to be more common in HTP than specific demographics such as a prior monotherapy.

1.6.3. Polypharmacy, Side effects and Co-Morbidity

The reasons why many of the heavily treated patients are in need of intensified treatment and the challenges that this intensified therapy regimen entails are very similar. Due to the advances in cART, infection with the HI virus is not life-threatening but has become a treatable condition. However, successful treatment requires daily medication which can be psychologically challenging. In addition, antiretroviral substances can cause a number of adverse effects which in turn can lead to further long-term effects and co-morbidities (Boyd & Hill, 2010). To manage side effects, additional medication is often necessary, leading to polymedication (Fernández Cañabate & Ortega Valín, 2019).

All of these factors are known to reduce patient adherence to the treatment regimen (Ammassari et al., 2002; Cantudo-Cuenca et al., 2014) and can consequentially lead to the development of resistant HIV strains. This development might in turn require a change or an intensification of treatment, leading to even more polymedication.

Heavily treated patients therefore face complex challenges: the factors that often caused their need for intense treatment continue to be the essential challenges in their ongoing treatment.

1.6.4. Compliance

Psychological distress and complexity of antiretroviral therapy were found to be associated with low adherence to therapy (Ammassari et al., 2002).

Patient's adherence, however, is of utmost importance for successful suppression of viral load. Adherence prevents further development of mutations and resistances; it decreases the risk of virological failure (Sethi et al., 2003). Thus, patient encouragement as well as the consideration of side effects are essential. The use of fixed-combinations to reduce the number of pills has been shown to increase compliance (Bangalore et al., 2007). In addition, modern substances, for example Maraviroc and Dolutegravir, are options that are potent in viral suppression and yet show comparatively mild side effects, increasing the likelihood of adherence on the patient's side (Elzi et al., 2017; van Lelyveld et al., 2016).

1.7. Aim of this Work

Antiretroviral therapy and number and effectiveness of available drugs has improved immensely since the discovery of HIV. Morbidity and mortality declined significantly, and HIV is now considered a chronic disease.

However, the HI virus shows unchanged mutation rates and therefore resistances to existing and new drugs will continue to develop. Hence, treatment failure still remains a reality. A considerable number of patients need an advanced treatment regimen because of an increasing incidence of multi-resistant virus strains (Aldous et al., 2017; Haggblom et al., 2016).
Knowledge about the subgroup of heavily treated patients is, however, limited. Conducting studies is often difficult due to a limited number of patients, and the available data on clinical and immunological consequences for heavily treated patients are inconclusive. Some studies found a worse prognosis for patients with a history of virological failure (Lohse et al., 2007; Lucas et al., 2004) and an increased mortality if a second virological failure occurs (Deeks et al., 2009). Yet, numerous patients might experience elevated viral loads while they remain healthy regarding immunological response and clinical symptoms (Deeks et al., 2000; Ledergerber et al., 2004). Reduced viral fitness, which, in some cases, results from viral mutations, might also be an advantage for these patients (Prado et al., 2005). Generally, available data are complex and further research is necessary to better establish care for heavily treated patients.

This thesis aims to investigate the sub-group of heavily treated HIV patients in relation to development and progression of neurocognitive impairment and motor functions.

HIV associated neurocognitive disorder, in contrast to most HIV associated diseases, does not show decreasing incidence, and remains highly relevant for clinical presentation of HIV patients even in the cART era (Heaton et al., 2011). Since data regarding this topic are scarce, this study's aim is to explore, whether advanced treatment of heavily treated patients shows an impact on their performance regarding neurocognitive and motor functions.

HIV patients in this study completed an extensive test battery consisting of neurocognitive and motor tests over a long period of time. To gain a better understanding of the effects associated with advanced treatment, the group of heavily treated patients were compared to a control group of HIV patients receiving standard treatment with three antiretroviral substances.

2. Methods

2.1. Study Design

This study was conducted with data from the HIV outpatient department of the Department of Neurology, University Hospital of Duesseldorf (1987-2020), with permission of the ethics committee under reference number 3666. It was designed as a prospective and retrospective cohort study.

All participants were patients with an HIV diagnosis. They presented for testing twice a year to evaluate their neurocognitive performance. At each visit, patients were asked about symptoms of metabolic syndrome, history of hepatitis, alcohol and drug use, as well as current CD4+ cell count and viral load, and their antiretroviral medication. Afterwards, all patients completed questionnaires and tasks regarding neurocognitive and motor function. These included International HIV Dementia Scale, Hamilton Depression Scale, Digit Symbol Test, Trail Making Test Part A and B, Regensburger Word Fluency Test, Stroop Color and Word Test, Grooved Peg Board Test, and motor function analysis (Arendt et al., 1990).

Completion of these questions and tasks took about 45 minutes per visit.

Additionally, at their first visit, the patient's intelligence quotient was determined through two different tests, the MWT-b (Lehrl, 1999) and the Standardized Progressive Matrices by Raven (Raven & Raven, 2003).

2.2. Questionnaires and Testing

2.2.1. International HIV Dementia Scale

Sacktor et al. (2005) developed a screening instrument to quickly assess an HIV patient's early symptoms of dementia. The test consists of three short tasks including memory and motor function. First, the instructor asks the patient to repeat and memorize four words: dog, hat, bean, and red (in this study mostly the German terms were used: Hund, Hut, Bohne, Rot). Next, the patient was instructed to spread thumb and index finger of the non-dominant hand and tap them onto the table alternatingly as fast as possible. This was demonstrated by the instructor. A score of zero to four was determined, depending on how many repetitions within five seconds could be achieved, while 15 repetitions were necessary for the full four points. The second task asked the patient to execute the Luria-Sequence as fast as possible with the non-dominant hand. The Luria-sequence entails three movements: 1. Place the hand onto the table in a fist, 2. Place the hand onto the table flatly, 3. Place the edge of the hand (ulnar side) onto the table. The instructor demonstrated this and let the patient practice two times. Then they evaluated how many

sequences the patient accomplished within ten seconds. The number of sequences represented the score. The third and last task was to repeat the four words memorized at the beginning. For each correct word the patient received one point, if assistance was necessary for a word, they received half a point. The points of all three tasks were added (maximum of twelve points). A score of ten or lower was categorized as pathological and interpreted as a first sign of HIV dementia.

2.2.2. Hamilton Depression Scale

Since depressive symptoms can overlap those of HAND, the 21-item Hamilton Depression Scale (Hamilton, 1960) was used to assess clinical depression. The instructor asked the patient a series of questions regarding thoughts, feelings and behavior, including sleep, suicidal ideation, feelings of guilt, capacity regarding daily activities and work, as well as somatic symptoms like pain, loss of appetite and sexual function. The corresponding items were 1-7, 12-14, and 16. Depending on the severity of the symptoms, zero to four points could be given per item, some only allowed up to two points. These points were divided into scores for guilt (item 2), suicide (item 3), work impairment (items 7 and 13), and depression (items 1, 4-6, 12, 14, 16).
Cronbach's alpha for the 21-item version is described to lie between 0.52 and 0.95, and correlation with clinical evaluations as a measure for external validity is between 0.70 and 0.95 (Hamilton, 1960).

2.2.3. Digit Symbol Test

Digit Symbol Test, part of the Hamburg Wechsler Intelligence Scale (HAWIE, Jacobs & Petermann, 2007; Wechsler, 1956), measures information processing speed with a high test-retest reliability between 0.80 and 0.89 (Strauss et al., 2006).
The patient received a paper sheet with four printed rows á 25 fields, containing the numbers one to nine in a varying order. Printed underneath each number field was an empty field. Above this area, each number was assigned a symbol, functioning as a key. The task was to draw the correct symbol underneath each number, completing as many fields as possible within a time frame of 90 seconds. Fields must be completed in the preset order. Time measuring started after the patient had completed the first seven fields which were meant for practice.
The number of completed fields equaled the score (maximum of 93) and was evaluated according to norms of the Wechsler test, adjusting for the patient's age. Additionally, the HAWIE score was noted. A percentile rank ≤ 16 as well as a HAWIE score ≤ 7 were categorized as pathological (see table 7 in the appendix).

2.2.4. Trail Making Test A and B

To determine information processing speed, the Trail Making Test (TMT) was used. It is part of the Halstead-Reitan Neuropsychological test battery though it can be implemented separately (TMT, Reitan & Wolfson, 1993).

In part A, the patient was asked to connect circles with numbers from 1 to 25 in ascending order while the instructor measures the time with a stopwatch. The numbers are irregularly distributed across the sheet. If drawn correctly, the connecting lines do not cross each other. Beforehand, the instructor demonstrated this on a separate sheet with the numbers 1 to 8. Any mistake during the test was corrected by the instructor immediately with time continuing to run, and the patient proceeded. Mistakes were not counted separately but were reflected in a longer completion time. The time was evaluated utilizing the norms by Tombaugh (2004).

External validity was considered to be high, correlations of test performance with brain injury, altered brain structure, and dementia were found repeatedly (Corrigan & Hinkeldey, 1987; Greenlief et al., 1985; MacPherson et al., 2017) and test-re-test reliability was reported as 0.79 for the TMT A and 0.89 for part B (Dikmen et al., 1999).

For the Trail Making Test Part B, testing executive function, the patient was now instructed to connect ascending numbers (1 to 13) and letters (A to L), alternating between both, e.g. 1 – A – 2 – B – 3 et cetera. Again, the numbers and letters were irregularly distributed across the sheet. If drawn correctly, the connecting lines do not cross each other. This principle was demonstrated on a separate sheet by the instructor. As with the TMT A, any mistake was corrected immediately, and time was taken during completion by the instructor. Evaluation was conducted using the norms provided by Tombaugh (2004), as seen in tables eight and nine in the appendix.

2.2.5. Regensburg Word Fluency Test

The Regensburg Word Fluency Test by Aschenbrenner et al. (2000) is designed to measure executive function as well as divergent thinking and consists of several subtests. They can be completed individually or as a compendium.

2.2.5.1. Semantic Categorial Fluency

In this subtest the patient was instructed to enumerate surnames beginning with any letter within the time frame of two minutes. Duplicates were not permitted. The instructor wrote down all mentioned names, disregarding the duplicates, and separating them into two columns, one for each minute. Afterwards, the names were counted, and scores were computed for the first

minute as well as for both minutes combined. The scores were then evaluated according to the norm tables (table 10 and 11 in the appendix), stratified for age and gender. A percentile rank ≤ 16 in the score for both minutes was classified as pathological.

2.2.5.2. Formal Lexical Word Fluency

In the subtest "formal lexical word fluency", the patient was asked to name words beginning with the letter "S" within a time frame of two minutes. Allowed were adjectives, verbs and nouns, though names, cities, countries and multiple composite nouns beginning with the same word (e.g. summer vacation, summer breeze, summer feeling) were not permitted. This was clarified through examples. The instructor wrote down all mentioned words, excluding non-permitted words and duplicates, separating those from the first and those from the second minute into different columns.

The words were counted for each minute, and a score was computed for the first minute and for both minutes combined. The latter was evaluated according to the table 12 and 13 (in the appendix), accounting for age and gender. A percentile rank ≤ 16 in the score for both minutes was classified as pathological.

2.2.6. Stroop Color and Word Test

The "Stroop Color and Word" test by Golden (1976), a measure for attention, includes three conditions: Word, Color and Color-Word. The patient received nine paper sheets, three for each condition. The patient was first asked to read words of colors printed in black (e.g. red, blue, green, yellow) from the first sheet. Next, in the color condition, a sheet with bars in different colors (red, blue, green, yellow) was presented to the patient and they were instructed to name the colors. Finally, the patient received a sheet with words of colors which were printed in a different color, for example the word "red" was printed in blue ink. The task was to ignore the written word and name the ink color. This sequence of the three conditions was repeated three times. For each of the nine sheets the time needed by the patient to complete the task was recorded by the instructor. While the word and the color condition required naming the word or color and served as control conditions, the word-color condition created interference and required concentration and attention. The automatic response was to read the written word, yet the task requires the participant to suppress this impulse and focus on the color.

After completion of all three rounds, the average time for each condition was calculated. The average time was then analyzed utilizing log- and t-values according to the table found in the appendix. Two scores, one for the word and color condition (naming) and one for the color-word

condition (interference) were computed. A score outside the values between 20 and 80 was considered pathological.
The Stroop Color and Word test is a commonly used instrument with reliability scores of 0.86 (word), 0.82 (color), and 0.73 (word-color) for individual testing (Golden, 1975).

2.2.7. Grooved Pegboard Test

The Grooved Pegboard Test (Trites, 1989) consists of 25 identical pegs with a ridge on one side and a physical board containing 25 corresponding holes, each orientated in a different direction. The patient was instructed to place the pegs into the holes one after the other, using only one hand which required manipulation of the peg with thumb and index finger. The test is designed to measure dexterity, which is linked to independency in the tasks of daily living (Williams et al., 1982). The peg sorting was then repeated with the other hand. During both repeats the instructor stopped the time needed.
The time was noted for both the dominant and the non-dominant hand and evaluated according to the norms by Ruff and Parker (1993). The norms (table 14 in the appendix) were differentiated by hand and age categories. A time of more than two standard deviations above the mean was considered pathological.
Stern et al. (2001) showed, as a measure for external validity, that a performance deficit in the Grooved Pegboard Test is associated with development of dementia in an HIV positive cohort. Another study found HIV positive patients with symptoms of HAND to be slower than healthy controls or HIV positive patients without HAND (van Wijk & Meintjes, 2015). Test-retest reliability was reported as 0.86 by Dikmen et al. (1999).

2.2.8. Central Motor Test Battery

Testing of central motor function has been established as a sensitive parameter for early detection of neurological progression in HIV patients (Nath et al., 1987). To screen for such developments the Hefter Central Motor Test Battery (Arendt et al., 1990) was constructed and later modified to better accommodate daily clinical application. This test battery focusses on fine motor skills which require a higher level of motor control. Therefore, a deterioration in this area can often be observed as a first sign of neurocognitive and motor dysfunction in patients with HIV.
Methods used to quantify the patient's fine motor skills include tremor frequency, most rapid alternating movements (MRAM) and most rapid voluntary isometric index finger extension (MRC)

including contraction time (CT), reaction time (RT), amplitude (AM) and rate of rise of tension (RRT = AM/CT).

Finger contraction time is a highly sensitive indicator for even preclinical central motor deficits (Arendt et al., 1989). Fingers are broadly represented in the primary motor cortex and have low muscle mass, therefore reducing interference of muscular activity with neurological function. A deficit in MRC serves as a surrogate parameter for an involvement of the central nervous system in HIV patients and often even precedes the development of clinical deficits in HAND (Berger & Arendt, 2000). Contraction time has been shown to be the most sensitive parameter in the motor skill test battery and is also suitable as a surrogate parameter regarding therapeutic success (Arendt et al., 1992).

2.2.8.1. Tremor

A light-weight accelerometer (PCB 308 B) was used to measure tremor frequency. It was placed first on the patients` right and subsequently on the left index finger. The patient then was asked to stretch out both arms in pronation and avoid movement for a duration of 25 seconds. The collected data was analyzed offline to determine the dominant tremor frequency in Hz, or tremor peak frequency. The analysis was based on a Fourier transformation using Spike 2 Software (by Science Products GmbH, Frankfurt a.M.).

2.2.8.2. Most Rapid Alternating Movement

The patient was instructed to place one hand and arm on the table and to stabilize the wrist with the other hand. Next, the patient was asked to extend the index finger and flex fingers D3 to D5. Over a timespan of 34 seconds, the patient now received instructions to flex and extend the index finger as rapidly as possible following the given command. The finger movements were recorded by the same aforementioned light-weight accelerometer (PCB 308 B) with modified configuration and subsequently analyzed offline. Again, a spectral analysis was used to determine maximum frequency of those “alternating movements”.

2.2.8.3. Most Rapid Voluntary Isometric Index Finger Extension

The most rapid voluntary isometric index finger extension (Arendt et al., 1990) are the most sensitive parameter measuring motor function.

The patient was asked to place the index finger in a ring of variable diameter that was closed tightly around the middle phalanx. A bi-directional force transducer was attached to the ring. Now, the patient placed headphones over his or her ears and was instructed, to extend his or her

index finger as fast as possible as soon as he or she heard an acoustic signal over the headphones. This signal was 50 milliseconds in length with a frequency of 1 kHz and was repeated 15 times in irregular intervals. Triggered by the acoustic signal, the connected computer recorded the patient's contraction for the duration of 1 second. The data acquisition was followed by an offline analysis, in which reaction time (RT, time between onset of signal and onset of movement), contraction time (CT, time between onset of contraction and maximum of contraction), force amplitude (AM), and rate of rise of tension (RRT = AM/CT) were computed. This sequence was performed for the index finger of both, right and left hand (Arendt et al., 1992; Arendt et al., 1990). For normal values see table 15 in the appendix.

2.3. Study population

2.3.1. Selection criteria

With respect to this thesis´ hypothesis, not all patients in the data bank were suitable for evaluation. In an attempt to eliminate known confounding factors, patients with a history of cerebral HIV associated opportunistic infections such as cerebral toxoplasmosis, cytomegalovirus infection, cryptococcosis and progressive multifocal leukoencephalopathy as well as intravenous drug abuse were excluded from the study. Furthermore, patients had to be on their current cART for at least six months, since neurocognitive improvement due to medication can be reliably observed after this time (Cysique et al., 2009).

2.3.2. Heavily Treated Patients and Controls

The group of heavily treated patients (HTPs) was defined as receiving five or more antiretroviral substances, at least two additional substances on top of a backbone regimen consisting of two NRTI plus either a PI, INI or NNRTI. The resulting combinations included patients with an existing backbone regimen, who receive two new substances, patients switching to a new backbone regimen and two additional substances, and patients who started on cART with five substances. These heavily treated patients were then categorized into those with detectable viral load (> 50 copies per ml blood) and those with undetectable viral load. Patients who received first line therapy, meaning two NRTIs plus either a PI, INI or NNRTI, served as controls. These were again categorized into those with detectable and undetectable viral load, resulting in a total of four groups: heavily treated patients with detectable viral load (HTP+), heavily treated patients with suppressed viral load (HTP-), controls with detectable viral load (controls+) and controls with suppressed viral load (controls-), see table 16.

Viral Load	Medication	
	Heavily Treated Patients *5 or more antiviral medications*	**Controls** *< 5 antiviral medications*
detectable *>50 copies/ml*	HTP+	Controls+
undetectable *<50 copies/ml*	HTP-	Controls-

Table 16: **Groups and Subgroups used for this study's statistical analysis**
HTP: heavily treated patients
ml: milliliter blood

2.4. Statistical Analysis

Statistical analysis was conducted using the mac version of IBM® SPSS® Statistics version 26. For further analysis groups were divided into four subgroups (table 16). To ensure each patient entered the analysis only once, only the results from each patient's first testing appointment included in the data set was used.

Demographic data were evaluated using mean values and frequency.

General assessment of group differences was conducted using Mann-Whitney U test comparing results in global scales in verbal function, executive function, information processing and motor function for the heavily treated patients. For a better differentiation of underlying effects several two-tailed T-Tests were performed for the heavily treated patients as well as for different combinations of the subgroups. In these cases, test results from each individual test were used. The two-tailed approach was favored because of the rather slim knowledge existing on this population. This allowed for detection of possible group differences in either direction. In case of insufficient homogeneity of variance, results from the Welch test were preferred.

Results $p < 0.05$ were interpreted as significant, setting the cut-off level at 95%.

A preliminary exploratory data analysis using Shapiro-Wilks test revealed a violation of the normal distribution assumption. However, since student's t-Test is known to deliver reliable results despite such violations (Bortz & Schuster, 2010) and a Mann-Whitney-U analysis provided similar results as the t-test, results of the t-test were included in this analysis. A multivariate analysis of variance was considered and omitted because several of the necessary assumptions were violated.

All graphs were created using Microsoft® Excel for Mac Version 16.40.

3. Results

3.1. Demographics

The study population demographic analysis was conducted for all six subgroups: heavily treated patients (HTP), control group (controls), heavily treated patients with elevated viral load (HTP+), heavily treated patients with suppressed viral load (HTP-), controls with elevated viral load (controls+) and controls with suppressed viral load (controls-). For complete results see table 17.

3.1.1. Sex

Male was the dominating sex in every group from 80 % in the controls+ group to 94.3 % in the HTP+ group. A similar distribution was found within the population of HIV patients in Germany (Robert Koch Institut, 2023). During the time span of data collection only male and female were accepted as sex categories and a diverse option was not available which is the reason behind a dichotomous representation of sex in this study.

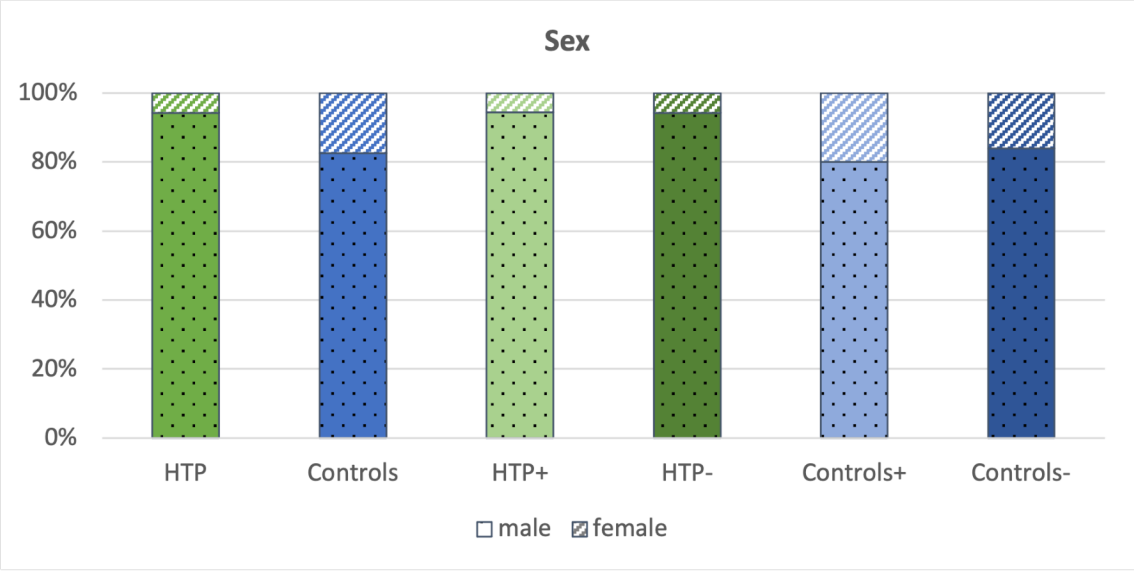

Fig 6: **Distribution of Male and Female Sex among the Subgroups**

HTP Controls HTP+ HTP- Controls+ Controls-

3.1.2. Age

The groups were balanced regarding age although female patients were younger across all subgroups. Controls+ was the youngest subgroup with 40.1 years while the oldest subgroup with 47.9 years on average was the HTP- participants.

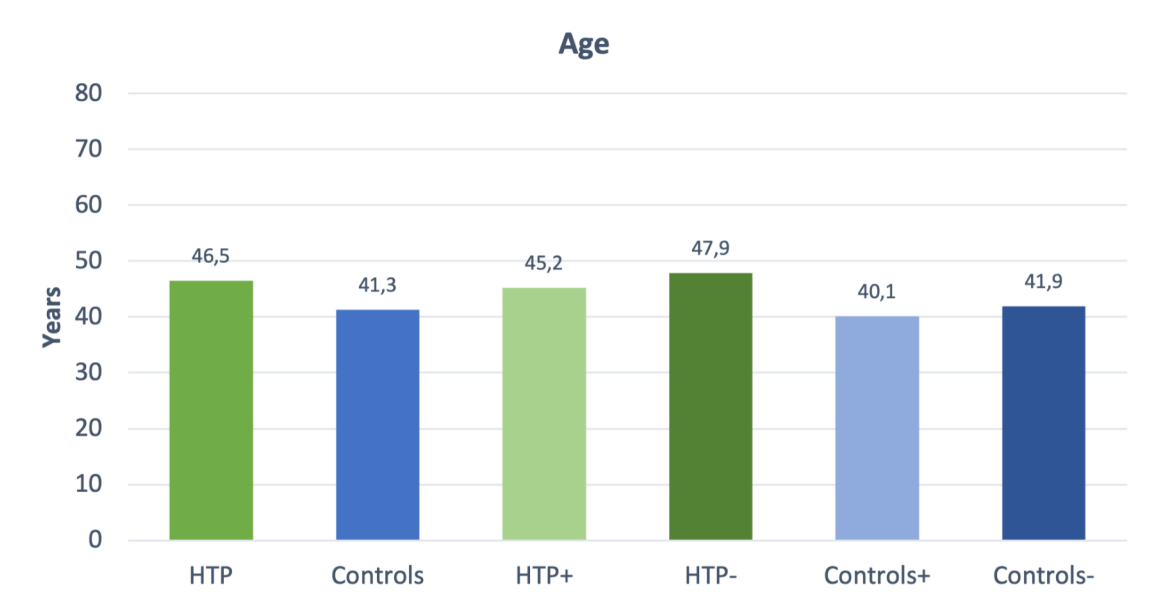

Fig 7: **Mean Age in Years across the Subgroups**

3.1.3. Duration of Illness

The heavily treated patients showed the longest time period between diagnosis and testing. While HTP had been living with HIV for an average of 122.8 months at the time of first testing, controls had been diagnosed 70.7 months prior to their first participation in this study. Controls with undetectable viral load had the shortest diagnose-to-testing interval with 67.9 months while HTP with undetectable viral load had been HIV-positive the longest with a duration of illness of 132.9 months on average. Patients who had been diagnosed less than six months ago had been excluded from the study prior to this analysis.

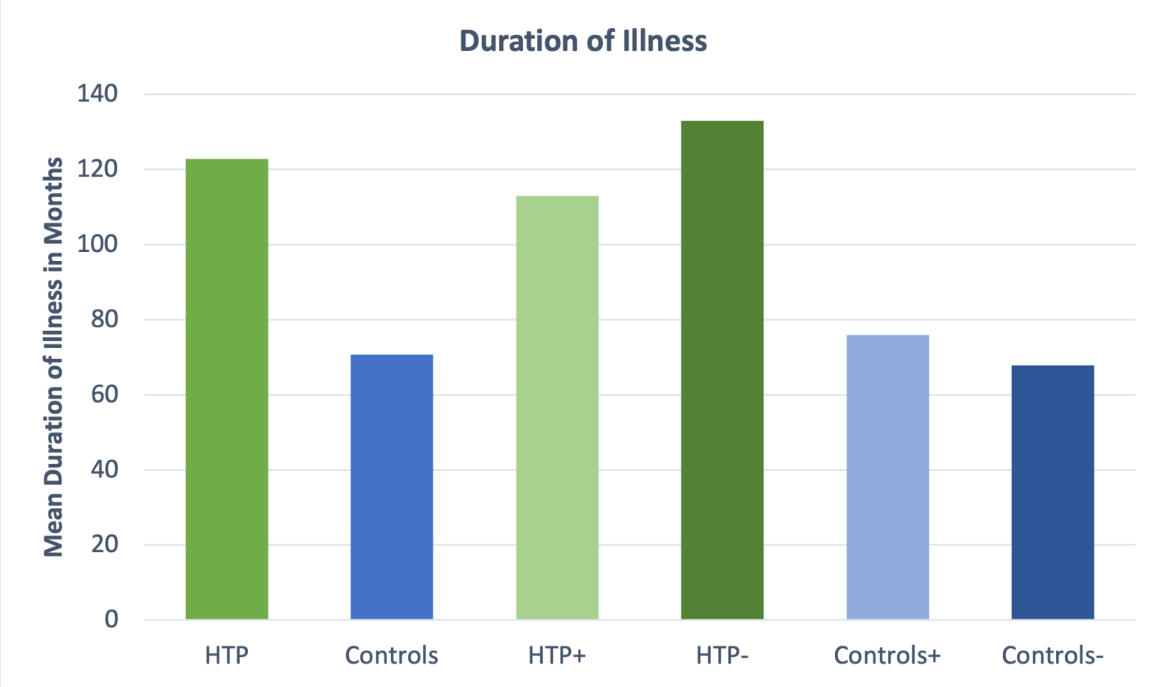

Fig 8: **Mean Duration between Diagnosis and Time of Study Participation**

3.1.4. Viral Load

Viral load was utilized as a differential criterion between subgroups, accounting for the differences found. The lowest viral load of 2.13 copies per ml was found in the control group with undetectable viral load. The highest average viral load was 62488 copies per ml in heavily treated patients with detectable viral load.

3.1.5. CD4+ Cell Count

The CD4+ cell count (figure 9) was considered as a measurement of overall health and virological control and split up into three categories from low (< 200 copies per ml) to medium (200 - 499 copies per ml) and high (> 500 copies per ml) (Deutsche AIDS Gesellschaft e.V., 2017a).
Heavily treated patients with undetectable viral load showed the lowest percentage in the low category (13.7%) and the highest percentage in high cell count (51.0%), displaying the overall healthiest CD4+ cell count among the subgroups. Heavily treated patients with detectable viral load displayed the highest percentage in low cell count (31.4%) and the lowest percentage of high CD4+ cell count (11.3%).
Controls with undetectable viral load were similar to the HTP with undetectable viral load while controls with detectable viral load showed comparable results to HTP with detectable viral load.

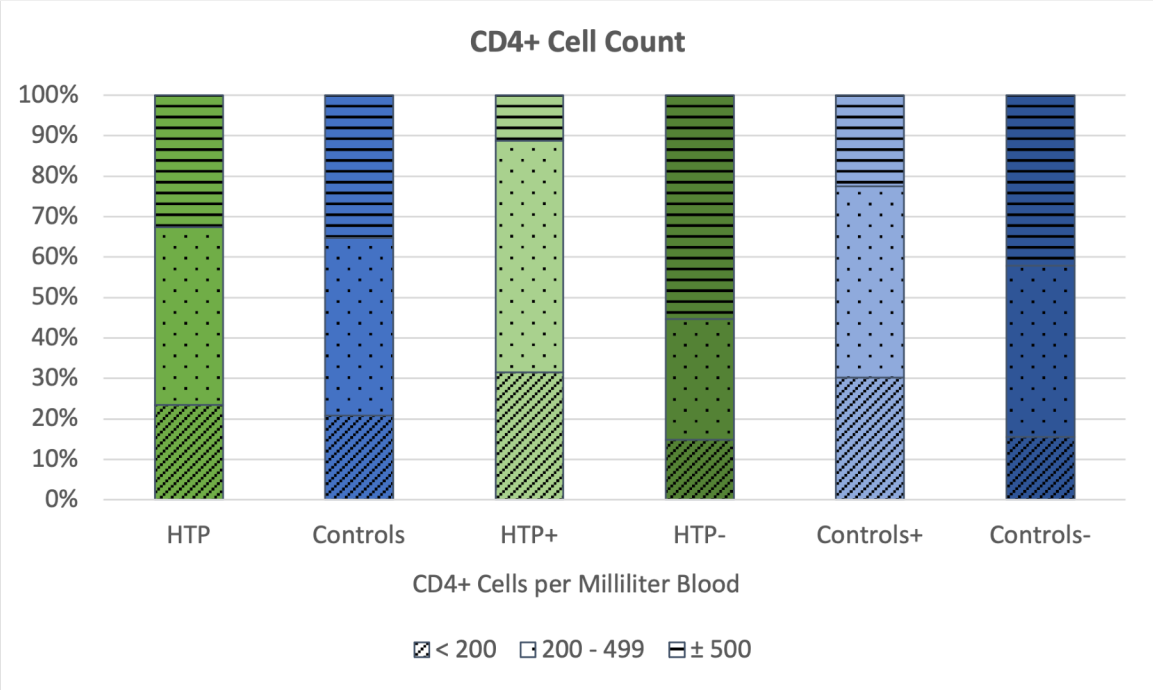

Fig 9: **Relative Distribution of CD4+ Cell Count across three Categories for each Subgroup**

HTP Controls HTP+ HTP- Controls+ Controls-

3.1.6. CDC Classification

Distribution of CDC stages varied between all subgroups as can be seen in figure 10. Heavily treated patients of all subgroups had progressed to a C3 stage more often than controls, especially heavily treated patients with detectable viral load.

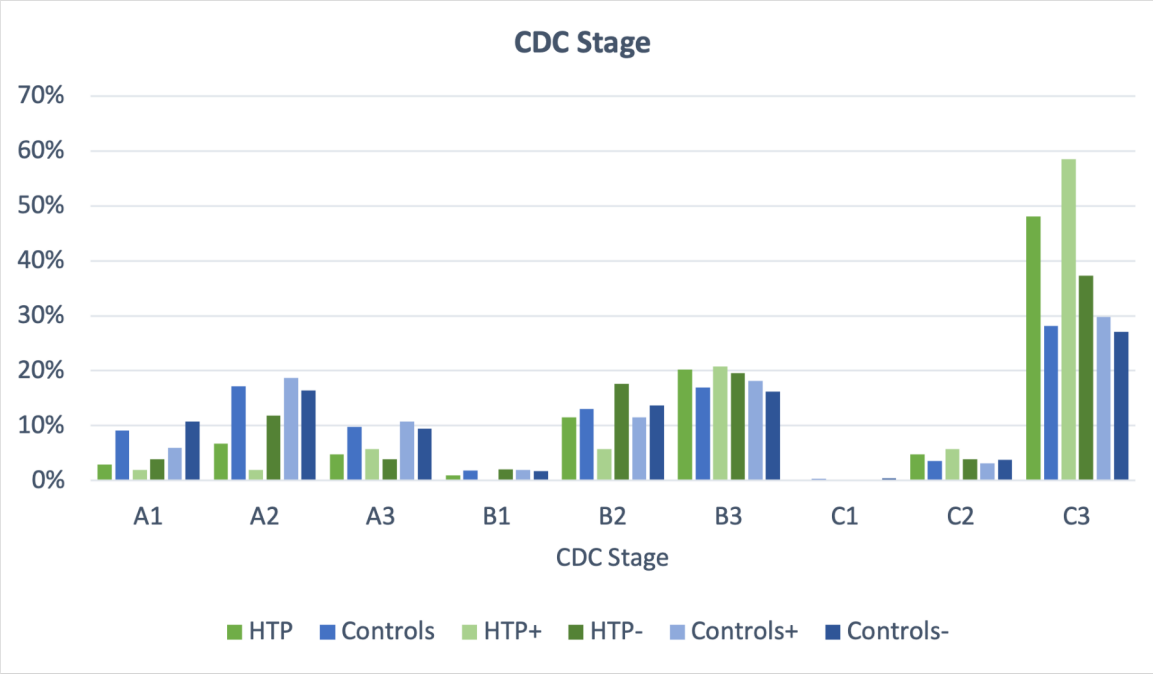

Fig 10: **Distribution across CDC Classification Stages among the Subgroups**

3.1.7. Risk Group

Homosexuals were the biggest risk group, followed by heterosexual and then bisexual patients. Hemophilia as an underlying risk factor for HIV infection was only present in the control groups. No heavily treated patient belonged to this risk group (see figure 11).

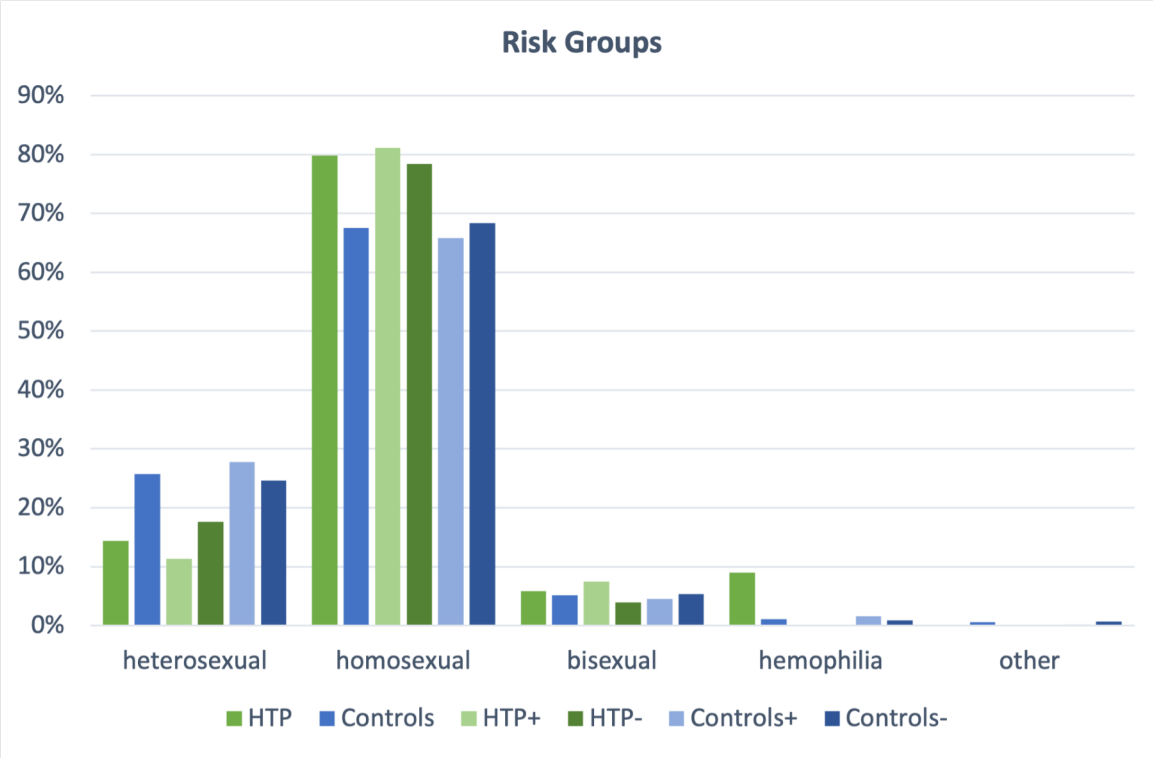

Fig 11: **Distribution across different Risk Groups for HIV across the Subgroups**

	HTP		Controls		HTP+		HTP-		Controls+		Controls-		unit
No. of Patients	**104**		**1404**		**53**		**51**		**486**		**918**		**n**
Age													
mean	46.5	*(9.1)*	41.3	*(9.7)*	45.2	*(8.6)*	47.9	*(9.5)*	40.1	*(9.3)*	41.9	*(9.9)*	**a *(± SD)***
mean male	46.9	*(9.1)*	41.9	*(9.5)*	45.4	*(8.7)*	48.5	*(9.4)*	40.7	*(9.0*	42.5	*(9.8)*	**a *(± SD)***
mean female	40.2	*(5.6)*	38.3	*(10.2)*	41.7	*(5.5)*	38.7	*(6.4)*	37.6	*(10.1)*	38.7	*(10.2)*	**a *(± SD)***
Sex													
male	98	*(94.2)*	1159	*(82.5)*	50	*(94.3)*	48	*(94.1)*	389	*(80.0)*	770	*(83.9)*	**n *(%)***
female	6	*(5.8)*	245	*(17.5)*	3	*(5.7)*	3	*(5.9)*	97	*(20.0)*	148	*(16.1)*	**n *(%)***
Duration of illness													
mean	122.8	*(64.9)*	70.7	*(57.1)*	113.0	*(59.2)*	132.9	*(69.4)*	76.0	*(56.1)*	67.9	*(57.4)*	**months *(± SD)***
CD4+ Cell Count													
< 200	23	*(22.1)*	283	*(20.2)*	16	*(31.4)*	7	*(13.7)*	146	*(30.0)*	137	*(14.9)*	**n *(%)***
200 - 499	43	*(41.3)*	597	*(42.5)*	29	*(56.9)*	14	*(27.5)*	225	*(46.9)*	372	*(40.5)*	**n *(%)***
± 500	32	*(30.8)*	480	*(34.2)*	6	*(11.3)*	26	*(51.0)*	109	*(22.4)*	371	*(40.4)*	**n *(%)***
CDC Stage													
A1	3	*(2.9)*	128	*(9.1)*	1	*(1.9)*	2	*(3.9)*	29	*(6.0)*	99	*(10.8)*	**n *(%)***
A2	7	*(6.7)*	242	*(17.2)*	1	*(1.9)*	6	*(11.8)*	91	*(18.7)*	151	*(16.4)*	**n *(%)***
A3	5	*(4.8)*	138	*(9.8)*	3	*(5.7)*	2	*(3.9)*	52	*(10.7)*	86	*(9.4)*	**n *(%)***
B1	1	*(1.0)*	25	*(1.8)*	0	*(0.0)*	1	*(2.0)*	9	*(1.9)*	16	*(1.7)*	**n *(%)***
B2	12	*(11.5)*	182	*(13.0)*	3	*(5.7)*	9	*(17.6)*	56	*(11.5)*	126	*(13.7)*	**n *(%)***
B3	21	*(20.2)*	237	*(16.9)*	11	*(20.8)*	10	*(19.6)*	88	*(18.1)*	149	*(16.2)*	**n *(%)***
C1	0	*(0.0)*	4	*(0.3)*	0	*(0.0)*	0	*(0.0)*	0	*(0.0)*	4	*(0.4)*	**n *(%)***
C2	5	*(4.8)*	50	*(3.6)*	3	*(5.7)*	2	*(3.9)*	15	*(3.1)*	35	*(3.8)*	**n *(%)***
C3	50	*(48.1)*	394	*(28.1)*	31	*(58.5)*	19	*(37.3)*	145	*(29.8)*	249	*(27.1)*	**n *(%)***
Viral Load													
mean	31846	(111086.5)	16984	*(76124.4)*	62488	*(149972.0)*	2.75	*(8.7)*	49062	*(123233.3)*	2.13	*(6.5)*	**copies/ml *(± SD)***
Risk group													
heterosexual	15	(14.4)	361	*(25.7)*	6	*(11.3)*	9	*(17.6)*	135	*(27.8)*	226	*(24.6)*	**n *(%)***
homosexual	83	(79.8)	948	*(67.5)*	43	*(81.1)*	40	*(78.4)*	320	*(65.8)*	628	*(68.4)*	**n *(%)***
bisexual	6	(5.8)	71	*(5.1)*	4	*(7.5)*	2	*(3.9)*	22	*(4.5)*	49	*(5.3)*	**n *(%)***
hemophilia	0	(0.0)	16	*(1.1)*	0	*(0.0)*	0	*(0.0)*	8	*(1.6)*	8	*(0.9)*	**n *(%)***
other	0	(0.0)	8	*(0.6)*	0	*(0.0)*	0	*(0.0)*	1	*(0.2)*	7	*(0.7)*	**n *(%)***

Table 17: **Overview of Demographic Data**

HTP = heavily treated patients, a = per year, SD = Standard Deviation, n = number, ml = milliliter

3.2. Interference statistics

3.2.1. Preliminary Analyses

To gain a general understanding of the data and the study population, an explorative analysis was performed comparing heavily treated with control patients. First, the Shapiro-Wilk test showed significant results for a majority of the tested variables, meaning the test results for heavily treated patients as well as for the controls were not normally distributed in regard to the tested variables. Additionally, outliers were found for most variables as well. Since HIV patients generally display a great variance with respect to test performance, outliers were included in the analysis nonetheless because they were assumed to be representative of their population.
Furthermore, assumptions for a multivariate analysis of variance were tested. In addition to the aforementioned univariate outliers and the distribution, Mahalanobis distance was calculated to determine multivariate outliers. No outliers were found ($p < 0.001$), albeit the distance could only be calculated for 37 of the 104 heavily treated patients due to missing data in one or more of the chosen variables. In addition, scatter plots revealed non-linear relationships for most variables. Although MANOVA is regarded as a reliable measurement even when its assumptions are violated, in this case it was decided against a multivariate analysis due to the considerably high number of violated assumptions.

For group comparisons of global scores the Mann-Whitney U test was chosen, since they were ordinally scaled. The same test was used to compare the occurrence of a pathological test score because of the dichotomous scale. For comparison of the individual neuropsychological tests as well as for the motor test battery subtests the two-tailed t-test was used, as well as the Welch test when indicated by a significant Levene test for homogeneity of variance.
For all tests a p-value of $p < 0.05$ was accepted as significant.

3.2.2. Global Scores

First, a Mann-Whitney U test was calculated comparing the scores for verbal function, executive function, information processing and motor function for heavily treated patients and controls. Since the scores were ordinally scaled, the two-tailed asymptotic results were preferred. As shown in figure 12, there was a statistically significant difference between HTP and controls in their motor function scores ($U = 64798.000$, $Z = -1.981$, $p < 0.05$) with a mean rank of 833.44 for heavily treated patients and 748.65 for controls. With respect to verbal function, executive function and information processing no significant group differences were found (verbal: $U =$

71379.500, Z = -1.349, p = 0.177, executive: U = 71812.000, Z = -1.315, p = 0.189, information: U = 72805.000, Z = -0.062, p = 0.951).

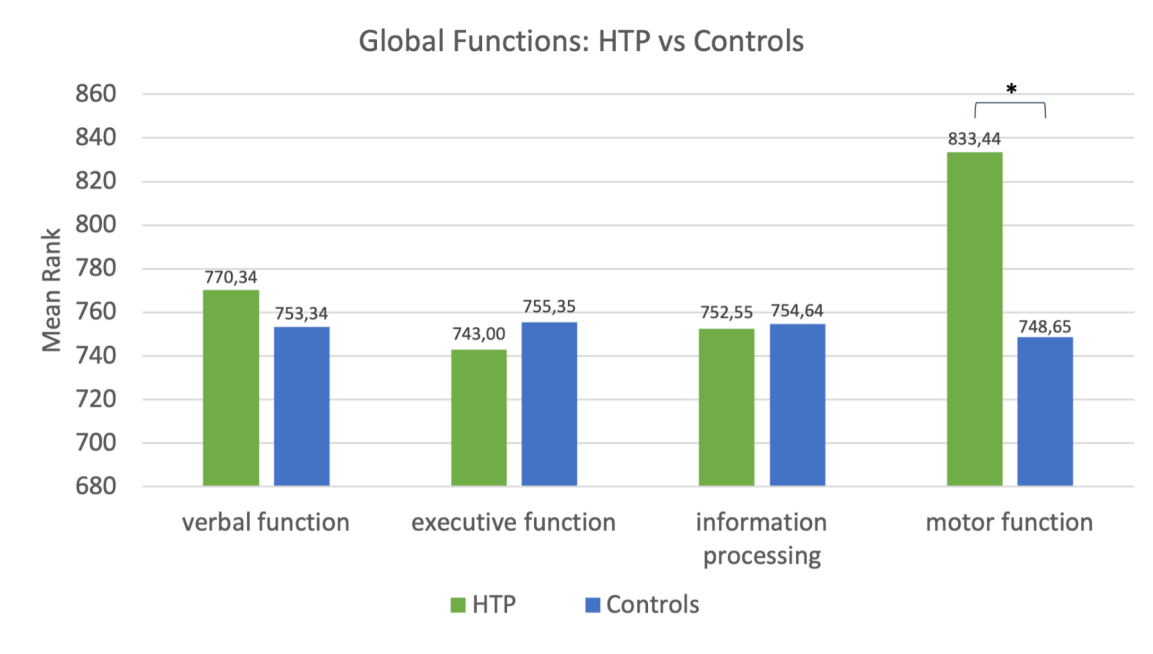

Fig 12: **Results of Mann Whitney U Test regarding global functions**
Comparison of mean ranks between heavily treated patients (HTP) and control group. HTP show a significant deficit in motor functions compared to the control group.
* = $p < 0.05$, significant group difference

3.2.3. Group Differences of Pathological Scores

As a more sophisticated approach, possible group differences with respect to the occurrence of a pathological test result were evaluated. Incidence of a pathological test result was noted for each test from the test battery and mean ranks compared using the Mann-Whitney U Test. The only significant group difference between heavily treated patients and controls was found for the MRAM of the right hand (U = 64636.000, Z = -2.644, $p < .01$) with a mean rank of 835.0 for the heavily treated patients and 748.54 for the control group. All other comparisons for HTP and controls did not reveal significant group differences neither for motor functions nor for neuropsychological tests.

3.2.4. Motor Function and Neuropsychological Testing

To further investigate the characteristics of the heavily treated patients, two-tailed t-tests were calculated for each test score. Table 18 shows the data of each comparison.

3.2.4.1. Heavily Treated Patients versus Controls

The t-test revealed significant group differences between HTP and controls for motor skills only, with one exception for the semantic word fluency score of the Regensburg Word Fluency Test. HTP showed a higher frequency in their MRAM (Fig. 13) for the right hand (mean = 6.6445, *SD* = 2.62, *t* (114) = 2.87, $p < 0.05$.) compared to the control group (mean = 5.8714, *SD* = 2.43). The Levene Test for homogeneity of variance, however, was significant, hence the values of Welch test were chosen. Additionally, the heavily treated patients displayed significantly higher values for the RRT (Fig. 14) for both, the right hand (mean = 38.33, *SD* = 18.14, *t* (1353) = 2.99, $p < 0.05$) and the left hand (mean = 38.14, *SD* = 18.92, *t* (1346) = 4.13, $p < .001$).

3.2.4.2. Heavily Treated Patients with and without detectable viral load

Next, focus lied on investigating whether or not viral load of different patient groups played a role. Therefore, heavily treated patients were subdivided in HTP with and without detectable viral load. In this comparison, significant group differences were found for Tremor of right (*t* (97) = -2.124, $p < 0.05$) and left hand (*t* (99) = -2.196, $p < 0.05$), see Fig. 15. In both cases the heavily treated patients with undetectable viral load showed a tremor with a higher frequency. They also appeared to have longer contraction time (Fig. 16) for both hands (right hand *t* (99) = -2.272, $p < 0.05$, left hand *t* (82) = -3.219, $p < 0.01$, using Welch test). The last significant group difference is the RRT for the right hand (*t* (99) = -2.673, $p < 0.05$) with the heavily treated patients with undetectable viral load showing a significantly higher RRT than HTP with detectable viral load. Although the difference regarding Tremor left between HTP and controls appears to be relevant enough to yield a significant group difference, analysis showed that this is not the case. The p-value is 0.781 for this comparison, presumably due to the large standard deviation of the control group (see table 18 below).

3.2.4.3. Detectable viral load: HTP versus controls

In the following, heavily treated patients are compared with controls, with both groups displaying detectable viral loads of more than 50 copies per ml. Here, only RRT for the left hand showed a significant group difference in motor skills (*t* (1626) = 2.932, $p < 0.05$) with HTP showing the higher RRT.

In addition, a significant difference was found for semantic word fluency using the Welch test (t (8) = 3.304, $p < 0.05$) with heavily treated patients achieving higher scores. This is the only case in which a group difference in non-motor skills could be shown.

3.2.4.4. Undetectable viral load: HTP versus controls

Completing the t-test analysis, heavily treated patients were again compared with controls, yet this time both groups showed undetectable viral loads. Heavily treated patients show a faster tremor of the right hand (t (3815) = 2.042, $p < 0.05$) but a lower score for MRAM of the right hand (t (50) = 2.043, $p < 0.05$, Welch Test). Similar to the comparison of all HTP and controls, RRT differs significantly for both hands. HTP show higher scores for both the right (t (3815) = 3.913, $p < 0.001$) as well as the left hand (t (3805) = 4.164, $p < 0.001$).

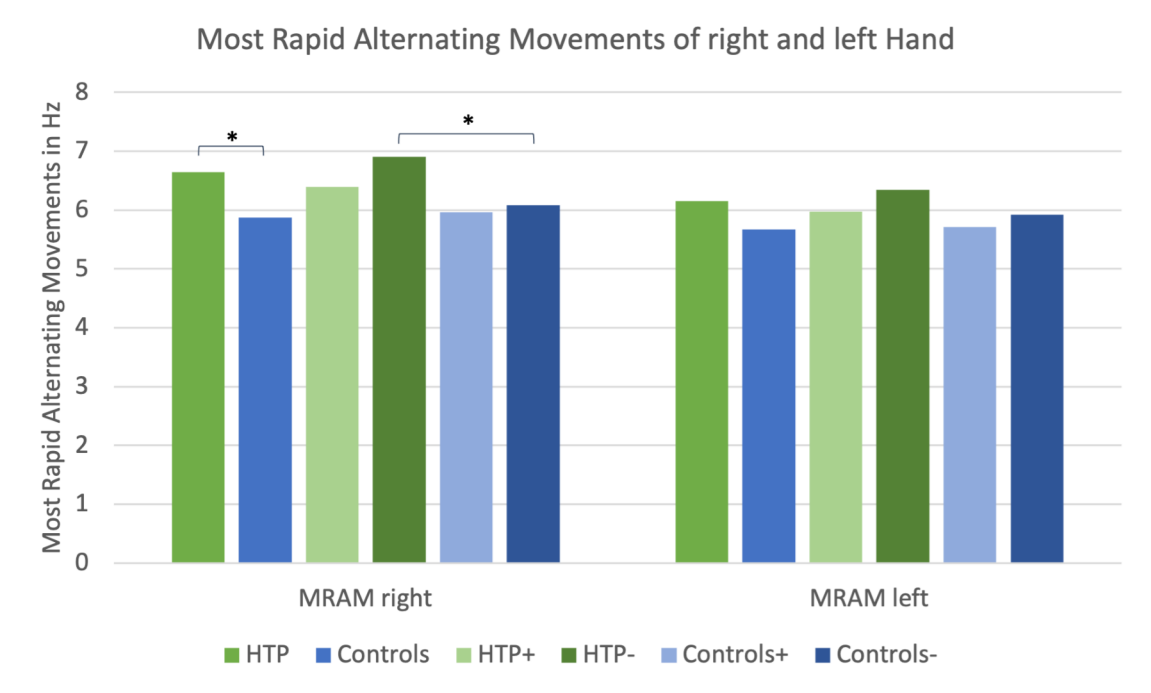

Fig 13: **MRAM for right and left Hand**
* = $p < 0.05$, significant group difference
Hz = hertz, MRAM = most rapid alternating movement, HTP = heavily treated patient

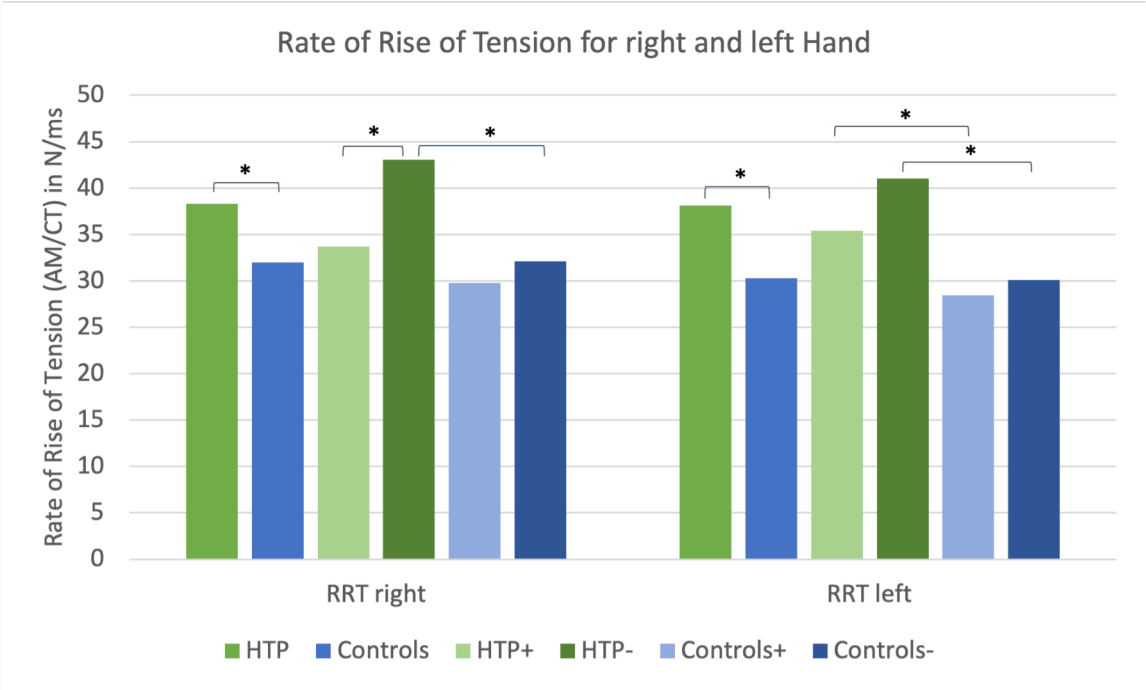

Fig 14: **Rate of Rise of Tension for right and left Hand**
* = $p < 0.05$, significant group difference
RRT = rate of rise of tension, AM = force amplitude, CT = contraction time

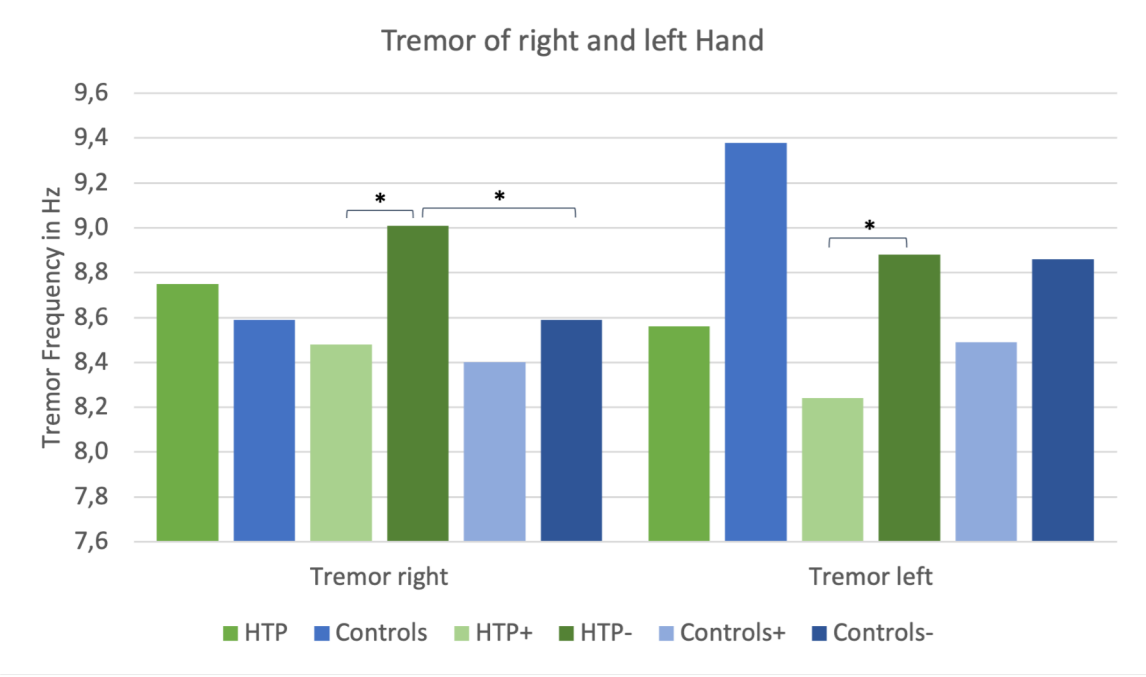

Fig 15: **Tremor for right and left Hand**
* = $p < 0.05$, significant group difference
Hz = hertz, HTP = heavily treated patients

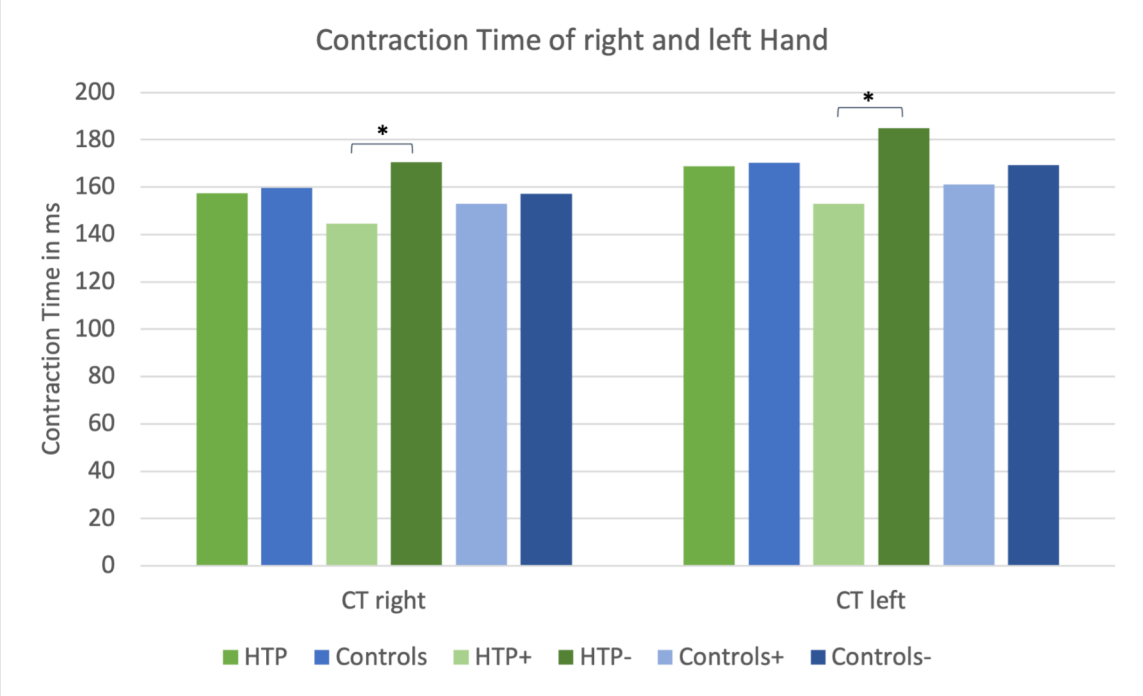

Fig 16: **Contraction Time for right and left Hand**
* = $p < 0.05$, significant group difference
CT = contraction time, ms = milliseconds, HTP = heavily treated patients

	HTP		Controls		p-value	HTP+		HTP-		p-value	HTP+		Controls+		p-value	HTP-		Controls-		p-value
	mean	*SD*	mean	*SD*		mean	*SD*	mean	*SD*		mean	*SD*	mean	*SD*		mean	*SD*	mean	*SD*	
Tremor right	8.75	*1.27*	8.59	*1.41*	0.277	8.48	*1.34*	9.01	*1.16*	**0.036***	8.48	*1.34*	8.40	*1.40*	0.700	9.01	*1.16*	8.59	*1.45*	**0.041***
Tremor left	8.56	*1.49*	9.38	*29.49*	0.781	8.24	*1.63*	8.88	*1.27*	**0.030***	8.24	*1.63*	8.49	*1.52*	0.254	8.88	*1.27*	8.86	*17.07*	0.993
MRAM right	6.64	*2.62*	5.87	*2.43*	**0.005***†	6.39	*2.37*	6.90	*2.84*	0.333	6.39	*2.37*	5.96	*1.96*	0.126	6.90	*2.84*	6.08	*2.15*	**0.046***†
MRAM left	6.15	*2.57*	5.67	*2.01*	0.072†	5.97	*2.07*	6.34	*3.02*	0.486†	5.97	*2.07*	5.71	*2.03*	0.351	6.38	*3.02*	5.92	*2.13*	0.332°
RT right	170.03	*41.41*	171.37	*61.29*	0.765	167.47	*43.32*	172.64	*39.64*	0.534	167.47	*43.32*	166.51	*53.96*	0.900	172.64	*39.64*	174.43	*59.03*	0.830
RT left	166.37	*41.63*	168.63	*60.86*	0.713	163.35	*41.20*	169.52	*42.26*	0.457	163.35	*41.20*	164.22	*52.57*	0.906	169.52	*42.26*	173.25	*62.46*	0.674
CT right	157.51	*58.82*	159.77	*63.18*	0.729	144.61	*40.62*	170.67	*70.91*	**0.025***	144.61	*40.62*	153.02	*53.46*	0.266	170.67	*70.91*	157.12	*56.77*	0.095
CT left	168.75	*51.96*	170.32	*68.17*	0.820	153.09	*37.34*	185.03	*59.85*	**0.002***†	153.09	*37.34*	161.05	*56.17*	0.143†	185.03	*59.85*	169.20	*62.25*	0.074
AMP right	6.96	*13.30*	8.94	*46.58*	0.671	4.57	*2.20*	9.39	*18.55*	0.068	4.57	*2.20*	4.56	*9.56*	0.994	9.39	*18.55*	59.81	*2057.32*	0.862
AMP left	7.19	*12.66*	9.15	*48.16*	0.682	4.97	*2.55*	9.49	*17.69*	0.072	4.97	*2.55*	4.28	*2.78*	0.074	9.49	*17.69*	10.24	*145.51*	0.971
RRT right	38.33	*18.14*	31.95	*20.82*	**0.003***	33.69	*15.61*	43.06	*19.43*	**0.009***	33.69	*15.61*	29.80	*17.42*	0.115	43.60	*19.43*	32.13	*19.63*	**<0.001***
RRT left	38.14	*18.92*	30.25	*18.54*	**0.000***	35.40	*17.45*	41.00	*20.11*	0.135	35.40	*17.45*	28.42	*16.86*	**0.003***	41.00	*20.11*	30.08	*18.39*	**<0.001***
Digit Symbol	52.17	*24.49*	51.49	*27.17*	0.906	57.33	*27.55*	49.07	*22.89*	0.436	57.33	*27.55*	54.12	*27.91*	0.736	49.07	*22.89*	55.83	*26.25*	0.322
GP dom	73.52	*30.55*	71.01	*21.74*	0.593	62.78	*10.10*	79.56	*36.48*	0.193	62.78	*10.10*	70.95	*18.76*	0.196	79.56	*36.48*	71.03	*19.60*	0.093
GP non-dom	80.28	*27.52*	76.56	*23.55*	0.456	68.56	*13.18*	86.88	*31.47*	0.112	68.56	*13.18*	78.39	*24.87*	0.241	86.88	*31.47*	77.12	*22.44*	0.236°
TMT1	42.95	*20.33*	45.21	*24.97*	0.697	49.00	*22.51*	35.56	*15.36*	0.145	49.00	*22.51*	47.47	*25.09*	0.835	35.56	*15.36*	44.39	*24.29*	0.277
TMT2	67.55	*23.19*	69.69	*38.13*	0.807	68.36	*17.47*	66.56	*29.90*	0.868	68.36	*17.47*	73.10	*33.03*	0.637	66.56	*29.90*	66.56	*33.69*	1.000
formal fluency	44.42	*32.99*	37.98	*25.93*	0.435	50.86	*34.64*	35.40	*31.93*	0.450	50.86	*34.64*	37.66	*26.33*	0.202	35.40	*31.93*	34.99	*25.98*	0.972
semantic fluency	66.17	*28.81*	52.29	*30.07*	0.133	77.86	*14.39*	49.80	*37.39*	0.173†	77.86	*14.39*	58.28	*29.48*	**0.010***†	49.80	*37.39*	52.22	*30.24*	0.860
Stroop TSEL	53.50	*6.28*	48.87	*44.84*	0.701	54.50	*7.43*	52.17	*4.67*	0.514	54.50	*7.43*	46.71	*18.07*	0.227	52.17	*4.67*	48.40	*26.28*	0.726
Stroop TNOM	52.00	*10.90*	45.61	*19.37*	0.230	49.25	*11.96*	55.67	*8.96*	0.293	49.25	*11.96*	47.34	*18.55*	0.774	55.67	*8.96*	48.14	*16.93*	0.278

* p-value < 0.05, significant group difference † Levene Test p < 0.05, reported value from Welch Test SD = Standard Deviation

Table 18: **mean values, Standard Deviation and p-value for t-Tests for all calculated group comparisons**, for abbreviations see page III and IV at the beginning of the thesis

4. Discussion

Heavily treated patients remain a minority and a small group among the HIV population. Hence, only a few studies focus on them.
They are one of the most vulnerable groups among HIV positive patients and therefore require attention of the scientific and medical community.
Heavily treated patients usually have a more advanced disease and are more likely to belong to CDC stage 3, as was this study population. Besides, multi-drug regimens are associated with a higher probability of comorbidities (Bailin et al., 2020; DAD Study Group et al., 2007; Taiwo et al., 2023). The defining characteristic for this patient subgroup is the need for extensive medication to reach viral load suppression. This is usually due to resistance development of one or more of the HIV strains. This resistance can be present from the very beginning or develop over time. Another reason for the necessity to deviate from standard therapy might be co-infections or comorbidities of the patient. Antiretroviral medication is subject to drug-drug interactions or might cause side effects. Therefore, a patient might not tolerate a standard regimen and thus might need an individualized treatment. In some cases, treatment regimens need to include more substances to achieve the best possible results, as seen in HTP.
The multi-drug approach, although sometimes necessary, is not without its problems. An increased number of drugs can cause an increased risk for drug-drug interactions and side effects, especially due to treatment of co-infections or co-morbidities. In addition, compliance and adherence to therapy regimen can be increasingly difficult with a higher number of drugs. Furthermore, psychological effects of poly-medication should not be underestimated.

Because of this vulnerability, it is necessary to dedicate resources and attention to heavily treated patients, to accommodate their treatment and support needs.
To evaluate whether a multi-drug approach might benefit these patients, more data regarding heavily treated patients are necessary. The aim of this work is to analyze data from heavily treated patients regarding their neurocognitive performance to learn more about cognitive reserve of this subgroup and the “neurological” cART effect.

Results of this study can be summarized as follows. First, there seems to be a slight deficit in motor functions in heavily treated patients in comparison to regularly treated HIV positive controls. Second, heavily treated patients and controls show comparable results regarding executive function, verbal function, and information processing, results confirming once more

former studies, revealing motor tests to be most sensitive in identifying neurological deficits and therapeutic success in HIV-patients (Arendt et al., 1992; Heaton et al., 2011).
This leads to the conclusion, that intensified treatment plays an important role in preserving cognitive function, especially the more complex functions.

4.1. Global Parameters and Pathological Scores

4.1.1. Global Parameters

4.1.1.1. Motor Function

The test battery used in this study included tests representing four areas of performance. Each test could be assigned to either verbal function, information processing, executive function, or motor function. A comparison of heavily treated patients with the control group showed a significant difference in regard to motor function but not concerning the other categories. Several studies proved that changes in motor function and precisely in fine motor function and motor speed are early signs of neurological changes in HIV patients (Arendt et al., 1990; Sacktor et al., 1996; von Giesen et al., 2005). Furthermore, pathological test scores in the motor test battery seem to have a predictive value for the development of HIV associated dementia (Arendt, 2007).
This difference hints towards a slightly more progressed disease state and a more severe neurocognitive deficit of the HTP population compared with the controls. This might have a number of underlying reasons:
First, demographic factors such as age or time elapsed since diagnosis could play a role.
HTP in this study are older and show a considerably longer period of time between diagnosis and testing. Both factors could contribute to their decreased performance regarding motor function. Motor function seems to be naturally deteriorating with age due to atrophy of the motor cortex and degeneration of neurotransmitter systems (Seidler et al., 2010), however, these findings are not based on age differences of a few months or years but compare motor skills over lifetime and refer to an aged population. The HTP in this study's population are slightly older but only by a few months. This suggests that age may not be the main contributing factor to motor performance differences.
Duration of illness, however, could play a significant role.
Several studies have observed that motor function declines in HIV positive patients even in with systemically stable infection. This degradation was shown to be associated with AIDS-related central nervous system disorders (e.g. infections), cerebrovascular disease and HAND (Robinson-Papp et al., 2020). Elicer et al. (2018) could show a decline in motor function over time in people living with HIV while cognitive functions remained stable.

Second, differences could be explained through the status as heavily treated patient and the associated socio-demographic factors. As mentioned in the introduction, heavily treated patients, although a relatively heterogenous group, face unique challenges. Compliance and adherence to the treatment plan might be a difficult endeavor for some of these patients (Bevilacqua et al., 2022; Zheng et al., 2022). It is known that resistance, a leading cause of polymedication in HIV patients, is often caused by non-adherence to therapy regimen (Benson et al., 2020). A patient with this history who is now receiving an even higher number of drugs, could be more likely to disregard the importance of close adherence to the cART regimen. In addition, psychological effects of the HTP status might contribute as well. Psychological stress has been shown to be a contributing factor to non-adherence, as is a complex treatment regimen (Ammassari et al., 2002).

Furthermore, the multidrug therapy itself might be a reason for this deficit in motor skill performance. Each medical substance brings not only benefits but also side effects. Antiretroviral drugs display a number of known side effects and interactions with each other, as well as with additional medication prescribed for different comorbidities (Reust, 2011). Patients with cerebral comorbidities were excluded from this study prior to data analysis, yet it was not possible to take every systemic co-morbidity into account. Therefore, drug side effects and interactions remain a factor that could play a role in the results.

Typical side effects do not directly relate to motor function and are therefore not likely to directly affect the tested variables. However, there are several studies implicating long term side effects as well. These are much more difficult to predict and control while nonetheless passively affecting the lives of HIV patients and their motor functions.

Several common side effects of cART are related to the cardiovascular system resulting in cardiovascular and cerebrovascular diseases - including myocardial infarct and stroke – which present a frequent cause of death in HIV patients (Croxford et al., 2017). Both, HIV infection and antiretroviral therapy, seem to act as separate risk factors, each increasing the chance of developing cardiovascular risk factors including hypertension, hypertriglyceridemia and lipodystrophy (Lorenz et al., 2008; Onen et al., 2010).

Similar to the increase in cardiovascular risk factors, Schröer et al. (2016) found that HIV patients show an increase in thickness of the intima media of the carotid arteries, a well-known predictor and risk factor for cerebrovascular disease. Furthermore, cART and HIV infection itself have been shown to be separate vascular risk factor (Gutierrez et al., 2017).

Cerebrovascular disease seems to be strongly associated with motor dysfunction in HIV patients, as Elicer et al. found in a study from 2018. This association appears to be even more substantial than the correlation between motor deficit and the patients´ HAND stadium (Elicer et al., 2018).

Therefore, an intensified antiretroviral therapy regimen might be a cause of a steeper or more rapid decline in motor function in heavily treated patients.
The aforementioned drug-drug interactions mainly relate to the metabolization using the liver's cytochrome P450 system (CYP). There are several well-known inducers and inhibitors of different CYP enzymes, each shortening or prolonging the metabolization process and therefore influencing drug availability in the body. Since these systems are complex and there are many different antiretroviral substances available, the possible combinations and interactions are many. In addition, non-antiretroviral co-medication could also influence metabolization and cause further interactions.

To summarize, there seems to be a slight difference in motor performance of HTP which can point to a more advanced disease state in these patients. Possible explanations can be polymedication, side effects including long-term cardiovascular disease as well as complex drug-drug interactions in antiretroviral substance as well as co-medications.

4.1.1.2. Executive Function, Verbal Function, and Information Processing

While there were significant results regarding motor function, there was no difference between the two groups regarding executive function, verbal function, or information processing.
The lack of difference within the scores for more complex functions could be interpreted as a neuroprotective effect of the intensified treatment regimen. Despite demographic differences, a more progressed disease stage, and a more complex treatment, heavily treated patients seem to be comparable to controls regarding higher cognitive functions. As other studies have shown, even in long-term HIV positive patients, cognitive functions seem to be stable while a decline in motor functions appears to be more common (Elicer et al., 2018; Robinson-Papp et al., 2020). In the treatment guidelines (Deutsche AIDS Gesellschaft e.V., 2017a) the "heavy treatment" approach is classified as an individual treatment plan and therefore no recommendation regarding substances is made. Resistance testing before treatment is strongly recommended, yet there is no guideline regarding the central nervous system effectiveness. A future study taking a closer look at the specific substances could clarify possible connections between heavily treated patients' performance and the CNS effectiveness of the chosen antiretroviral substances. Such studies would have to take CNS effectiveness score (CPE) (Letendre et al., 2008) into account.

4.1.2. Pathological Scores

A similar argument as with the global scores can be made for comparison of the number of pathological test results.

It was determined for each test, how many of the test results were categorized as pathological for heavily treated and control patients, respectively. Controls outperformed HTPs regarding most rapid alternating movements (MRAMs) of the right hand. This is in agreement with results for global scores reported above. Yet, since a significant difference was found only for MRAM of the right hand and not for other tests of motor function, it also might hint that a more differentiated approach might be useful, for example taking dexterity into account.

4.2. T-Tests

Student's T-Test were calculated to closer examine the possible differences between the study's groups. As could be expected from the results for the global variables, group differences mainly occurred for variables testing motor function and not for variables measuring more complex concepts such as executive or verbal function.

4.2.1. All HTP versus All Controls

Heavily treated patients seem to perform faster and therefore better than the control group regarding the most rapid alternating movements as well as the rate of rise of tension. This is surprising and seemingly contradictory to the results of the global scores and the number of pathological scores mentioned right above.

A possible explanation could be the heterogeneity of study groups. A closer look at the data reveals a considerably large standard deviation for the rate of rise of tension for both groups. Hence, this indicates that a much larger group size would be necessary for reliable results. Due to the study design, the small number of patients is certainly one of the study's greatest limitations.

4.2.2. Heavily Treated Patients: detectable and undetectable viral load

Heavily treated patients remain a marginalized group within the HIV population. A detailed look at this population and their characteristics is therefore a key element of this study.

Since viral load is the most important surrogate marker for therapy success, heavily treated patients were divided into those with detectable and those with undetectable viral load.

Again, group comparisons showed no specific general trend. While patients with an undetectable viral load performed better regarding rate of rise of tension, they were surpassed by the patients with elevated viral loads concerning tremor frequency and contraction time. One possible influence could be the demographic differences between the groups. Heavily treated patients with elevated viral load are younger and have a shorter duration of illness than patients with undetectable viral load. This leads to the assumption that the HTP+ group has yet to find an effective therapy regimen but is overall "healthier". This is, however, not supported when looking at the CDC stage. Here, a majority of HTP with elevated viral load is in the CDC C3 stage (58.5%) compared to only 37.3% of HTP with undetectable viral load. To summarize, while demographic differences might seem plausible as an explanation for the differences in motor skills, a closer examination reveals the connection is not so clear.

This might be an indication that viral load alone might not be sufficient as an exclusive surrogate parameter for therapy success in highly specific subgroups such as heavily treated patients. As discussed above, the characteristics of heavily treated patients are complex and so are the implications of a multi-drug therapy regimen. Heavily treated patients often suffer from comorbidities and require additional medication and treatments on top of their antiretroviral therapy. They take a minimum of five drugs a day and usually more, each drug being a risk for interactions and side effects. In these cases, a more detailed evaluation of therapy success, maybe including a score for motor function might be more accurate.

4.2.3. Elevated viral load: HTP versus controls

While it is possible that viral load might not be the ideal surrogate parameter to measure therapy success in heavily treated patients, it remains an important marker to evaluate study results. Therefore, one section of this study focused on subgroup differences of heavily treated patients and controls with elevated viral loads. The main question was whether there were remaining differences between HTP and controls when differences in viral load were taken out of the equation. What could be observed was a better performance of heavily treated patients regarding rate of rise of tension as well as in semantic word fluency with both groups having detectable viral load. While this still might be a result of chance and therefore neglectable on a population level, it might also be an indicator that a multi-drug approach actually could be beneficial.

The concept behind a multi-drug approach is to attack the virus on multiple levels. In heavily treated patients specifically the aim is to reach and control all viral strains to avoid development and replication of resistant variants. We see this approach not only in antiretroviral therapy but also in several other fields in medicine. It is the case in broad spectrum antibiotics for critical illnesses, for example sepsis, meningitis or tuberculosis (Arbeitsgemeinschaft der

Wissenschaftlichen Medizinischen Fachgesellschaften e. V., 2018) or the approach of heterologous vaccination as with Ebola (Mutua et al., 2019) or, in some cases today, even Sars-CoV-2 (Robert Koch Institut, 2021). These are examples of high-risk situations with the aim of 'hitting hard and early' and de-escalating later on. It is important, however, to de-escalate as soon and as extensively as possible, to avoid unnecessary side effects and risk of cultivating resistances. A different aspect of the multi-drug regimen is that it is more likely to attack not only all viral strains but also all compartments where viral copies might be found – specifically the central nervous system. There is increasing interest in the properties of specific drugs and specifically the ability to penetrate the blood brain barrier. As mentioned earlier, development of HIV associated dementia or HAND is due to HIV crossing the blood-brain barrier. If a combination therapy of five or more substances is prescribed, there is an increased probability that at least one substance has a high CNS penetration capacity, usually classified by CPE score (Central Nervous System Penetration Effectiveness Score). Vogt (2019) assumed a stabilizing effect of antiretroviral substances with a high CNS penetration score on neurocognitive and motor function in HIV patients. Generally, CPE is still subject to debate since existing data are relatively scarce and contradicting. Nowadays, the topic is less important, because almost every cART combination exceeds the minimum CPE score of 7.

4.2.4. Undetectable viral load: HTP vs controls

To complete discussion of possible associations between viral load and heavily treated patients, this subsection examines the differences of heavily treated patients and controls when both groups show an undetectable viral load. In other words, these are patients who reached the defined treatment goal of undetectable viral load. Similar to other discussion points, results regarding the group differences are mixed. Under optimal therapy, control patients outperform heavily treated patients with respect to most rapid alternating movements as well as tremor frequency. Yet, the rate of rise of tension is steeper in heavily treated patients.
It has been shown that MRAMs are influenced by patient co-operation, so MRAMs are the most variable parameter of the motor test battery, susceptible to effects of patient participation. Similar to the other sub-analyses, there seems to be a slight deficit in motor function of heavily treated patients in comparison to HIV positive controls, yet the results keep hinting to the complexity of the interactions and the complexity of heavily treated patients as a subpopulation.

4.3. Conclusion and Limitations

Heavily treated patients are a special and often neglected subgroup of the HIV population. The aim of this study was to better characterize this group with respect to their treatment and possible benefits of the intensified treatment regimen. The focus was directed towards neurocognitive performance and motor skills, as motor function seems to be an early predictor of neurocognitive decline in HIV patients and hence predictive of the overall outcome and mortality in HIV patients (Naveed et al., 2021).

After approaching these questions from different points of view to detect possible correlations and connections, no marked differences could be shown; yet there seems to be a tendency for a slight deficit in motor function. It appears, that heavily treated patients achieve very similar overall outcomes to the control group, except for a difference in the global motor score and several sub-scores of motor function.

As stated in the guidelines for combined antiretroviral therapy, the therapy aim is an undetectable viral load of less than 50 copies per ml blood since this has been shown to reduce mortality and increase the patients' quality of life as well as life expectancy. In heavily treated patients, there exists a necessity to use a combination of five or more different antiretroviral substances to achieve this goal.

Considering this information, to achieve a comparable neurocognitive and motor function outcome in "heavily treated" and "regularly treated" HIV patients can be considered a success. Nonetheless, the data regarding global scores showed a tendency of poorer performance of heavily treated patients regarding motor function. This tendency should be taken seriously. A decline of motor skill is considered to be an early and sensitive sign for disease progression and therefore should be classified as an important therapy monitoring parameter.

Some results of this study point out that viral load might not be an ideal predictive factor for motor skill performance, at least not in the heavily treated HIV population. This might be an indication, that analogue to their complex characteristics heavily treated patients could benefit from a more complex monitoring regarding their medication needs.

Since there is not extensive research regarding the subpopulation of heavily treated patients and to address the complexity in a patient-centered and evidenced based way, additional research is necessary.

Limits of this study include the clinical study setting and the retrospective approach. Since there is a very limited amount of data regarding heavily treated patients, this study was designed as an exploratory analysis to detect further questions and hypotheses and help inform future research.

This approach excluded some statistical methods that might have been helpful in detecting additional correlations and connections.

Furthermore, the number of participants in the group of heavily treated patients was relatively small, especially in comparison to the control group. This is due to the nature of this subpopulation being a specialized group and matches the distribution within the population of HIV patients. A study with more participants or a matched cohort could yield more representative and more differentiated results. We hope to see further research on heavily treated patients in the future.

Overall, heavy treatment with five antiretroviral substances for HIV patients who otherwise cannot achieve suppression of viral load in blood seems to be a successful approach in improving these patients' lives. The approach is not without risks and often applied in patients with comorbidities or resistant viral strains. Because of the complexity of the patient cohort and the intensity of the treatment setup, it should be carefully planned and monitored, taking all aspects of the patient's medical history as well as personal needs and preferences into account.

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Appendix

Digit Symbol Test

	age of patient								
PR	**18-19**	**20-24**	**25-34**	**35-44**	**45-54**	**55-64**	**65-69**	**70-74**	**HAWIE**
<1	0-7	0-9	0-4	0-4	0-4	0-3	0-3	0	**1**
<1	8-14	10-14	5-11	5-10	5-12	4-11	4-8	1	**2**
1	15-20	15-23	12-23	11-18	13-16	12-15	9-11	2-4	**3**
2	21-26	24-28	24-28	19-26	17-20	16-18	12-15	5-7	**4**
5	27-32	29-33	29-33	27-30	21-24	19-22	16-18	8-11	**5**
9	33-37	34-38	34-38	31-34	25-28	23-25	19-22	12-14	**6**
16	38-43	39-42	39-42	35-38	29-31	26-29	23-25	15-18	**7**
25	44-48	43-48	43-46	39-42	36-39	33-36	26-28	19-21	**8**
37	49-54	49-52	47-50	43-46	36-39	33-36	29-32	22-24	**9**
50	55-59	53-57	51-54	47-50	40-42	37-39	33-35	25-28	**10**
63	60-65	58-61	55-58	51-54	43-46	40-43	36-39	29-31	**11**
75	66-69	62-66	59-62	55-58	47-50	44-47	40-42	32-35	**12**
84	70-71	67-71	63-66	59-62	51-54	48-50	43-46	36-38	**13**
91	72-74	72-76	67-70	63-66	55-57	51-54	47-49	39-42	**14**
95	75-77	77-80	71-74	67-70	58-61	55-57	50-53	43-45	**15**
98	78-79	81-85	75-78	71-74	62-65	58-61	54-56	46-49	**16**
99	80-82	86-90	79-82	75-78	66-68	62-64	57-60	50-52	**17**
>99	83-85	91-92	83-86	79-82	69-71	65-68	61-63	53-56	**18**
>99	86-93	93	87-93	83-93	72-93	69-93	64-93	57-93	**19**

Table 7: **Norms for Digit Symbol Test**
Number of completed fields within 90 seconds converted into the respective percentage range per age group
PR: percentage range

Trail Making Test Part A and B

	age of patient					
PR	**20-39**	**40-49**	**50-59**	**60-69**	**≥ 70**	
10	50	59	67	104	168	sec
25	42	45	49	67	105	sec
50	32	34	38	48	80	sec
75	26	28	29	35	54	sec
90	21	27	25	29	38	sec

Table 8: **Norms for Trail Making Test Part A**
Completion time in seconds converted into the respective percentage range per age group.
PR: percentage range

	age of patient					
PR	**20-39**	**40-49**	**50-59**	**60-69**	**≥ 70**	
10	129	151	177	282	450	sec
25	94	100	135	172	292	sec
50	69	78	98	119	196	sec
75	55	57	75	89	132	sec
90	45	49	55	64	79	sec

Table 9: **Norms for Trail Making Test Part B**
Completion time in seconds converted into the respective percentage range per age group.
PR: percentage range

Regensburger Word Fluency Test

1 minute testing time						**2 minutes testing time**				
Age groups						**Age groups**				
18-29	30-41	42-53	54-65	>65	**PR**	18-29	30-41	42-53	54-65	>65
18	17	15	15	6	**10**	28	29	28	25	12
19	17	16	16	8	**16**	29	29	28	27	15
20	19	17	17	12	**25**	32	31	29	29	18
23	24	20	20	18	**50**	36	37	34	33	27
28	27	23	21	23	**75**	43	42	38	36	38
30	29	24	24	24	**84**	44	46	41	38	39
32	30	27	26	24	90	46	48	44	39	41

Table 10: **Norms for Regensburger Word Fluency Test, Semantic Categorial Fluency, male patients**
PR: percentage range

1 minute testing time						**2 minutes testing time**				
Age groups						**Age groups**				
18-29	30-41	42-53	54-65	>65	**PR**	18-29	30-41	42-53	54-65	>65
19	19	17	16	7	**10**	33	33	26	28	14
22	21	18	18	11	**16**	35	34	30	29	18
22	21	21	19	12	**25**	38	36	33	32	22
25	27	24	22	16	**50**	42	42	38	35	28
31	30	29	25	23	**75**	52	48	45	39	32
33	31	30	28	24	**84**	56	50	49	44	40
35	33	31	29	24	**90**	60	53	50	46	44

Table 11: **Norms for Regensburger Word Fluency Test, Semantic Categorial Fluency, female patients**
PR: percentage range

1 minute testing time						**2 minutes testing time**				
Age groups						**Age groups**				
18-29	30-41	42-53	54-65	>65	**PR**	18-29	30-41	42-53	54-65	>65
9	12	9	8	6	**10**	15	17	16	10	9
11	13	11	9	6	**16**	16	20	17	13	10
12	14	12	10	8	**25**	19	22	19	15	12
16	16	15	13	10	**50**	25	26	26	21	18
19	19	20	16	13	**75**	32	31	33	26	25
22	21	22	18	17	**84**	33	33	35	30	25
24	23	24	20	19	**90**	35	34	38	37	30

Table 12: **Norms for Regensburger Word Fluency Test, Formal Lexical Word Fluency, male patients**
PR: percentage range

1 minute testing time						2 minutes testing time				
Age groups						Age groups				
18-29	30-41	42-53	54-65	>65	**PR**	18-29	30-41	42-53	54-65	>65
11	11	10	10	4	**10**	17	18	14	16	7
13	12	10	11	4	**16**	19	20	16	18	9
14	13	11	12	6	**25**	22	21	17	20	10
17	16	14	15	11	**50**	29	25	22	24	16
20	20	18	18	15	**75**	32	30	27	29	24
21	22	19	18	17	**84**	34	33	29	30	28
22	23	21	21	19	**90**	35	37	33	32	30

Table 13: **Norms for Regensburger Word Fluency Test, Formal Lexical Word Fluency, female patients**
PR: percentage range

Grooved Peg Board Test

	dominant hand			non-dominant hand			
age	**in mean**	**1 SD**	**2 SD**	**in mean**	**1 SD**	**2 SD**	
15-19	66.05			70.50			sec
20-29	63.40			69.10			sec
30-39	62.95	71.35	79.75	67.15	79.35	91.55	sec
40-49	63.50	70.70	77.90	69.05	78.85	88.65	sec
50-59	68.10	75.52	86.94	74.50	85.21	95.72	sec
≥ 60	82.70	101.40	129.18	87.95	114.15	140.85	sec

Table 14: **Norms for Grooved Peg Board Test**

Most Rapid Voluntary Isometric Index Finger Extensions

	normal range	
Tremor	8 - 12	Hz
MRAM	6.0 - 8.0	Hz
RT	100 - 180	msec
CT	120 - 140	msec

Table 15: **Norms of Most Rapid Voluntary Isometric Index Finger Extensions**
(Arendt et al., 1992)

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