

STUDY PROTOCOL: INFZ-ZPHI-01.01**“Characterization of acute and recent HIV-1 infections in Zurich: a long-term observational study.”**

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1. Summary

Aim of the study: To describe the epidemiology, longitudinally follow, test the effect of early antiretroviral treatment and investigate early events of virus-host interactions in patients with documented acute or recent HIV-1 infection in Zurich.

Study design: This is an open label, non-randomized, observational, monocenter study at the University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology. We aim at enrolling approximately 300 patients over a 10 year period. All patients who fulfill the inclusion criteria of a documented acute or recent HIV infection can participate in the study. Patients are offered early combination antiretroviral treatment (cART), if treatment start falls within 90 days after diagnosis of acute HIV-infection. After one year of suppressed HIV-plasma viremia (< 50 copies/ml) patients can chose to stop cART. Patients who have not chosen to undergo early-cART, respectively will stop cART after one year will be followed for a total of 5 years. Viral setpoints reached after treatment interruptions will be compared to historic controls and to the control group not having received cART during acute infection. A battery of virological and immunological assays will be performed on blood samples obtained to better understand early virus-host interactions, which are thought to play a key role in HIV-pathogenesis research.

Summary: In summary, this study will provide comprehensive knowledge on early HIV-infection with regard to epidemiology, impact of early-cART on the course of disease and forms the base for a variety of translational research projects addressing early key pathogenesis events between virus and host, relevant for the course of disease, for transmission, for development of vaccines and new treatment strategies.

2. Introduction

Background

Twenty years after emergence of the AIDS epidemic and a decade after introduction of highly successful combination antiretroviral therapy (cART) HIV-1 remains one of the three leading infectious diseases in the world causing a high burden of morbidity, mortality and costs [1, 2].

Despite an enormous body of knowledge accumulated, a number of key questions regarding HIV-pathogenesis remain unresolved. To date it is still not fully understood what factors determine the viral setpoint in a given individual. Even less is known about factors determining viral transmission. It has been recognized that longitudinal studies of HIV-infected patients early on after primary HIV infection (PHI) may be key to better understanding of HIV-pathogenesis [3-8]. Insights of early events between virus and host may potentially be crucial for development of vaccines, new drugs, microbicides and new strategies optimizing long-term antiretroviral therapy. Despite 10 years of cART to date it remains unknown whether early-cART initiated during PHI can alter the course of disease in delaying disease progression [5, 9-14].

Thus, taken together there is a strong need for systematic longitudinal pathogenesis studies in humans infected with HIV-1 addressing transmission and early virus-host events.

Early antiretroviral treatment after primary HIV infection.

The optimal time to start antiretroviral therapy for HIV-infected patients remains unknown [15-18]. Even less clear is whether treatment of PHI early on is beneficial in terms of delaying disease progression. Recent work provided some rationale that early intervention during PHI might indeed be beneficial. Yerly et al. [19], demonstrated that viral rebound and setpoint upon interruption of cART in chronically infected patients is predicted by proviral DNA levels at time of treatment stop. Furthermore, Strain et al. [20] showed that reduction of the size of the latent reservoir is significantly more pronounced in early-cART treated PHI patients when compared to initiation of cART in chronic infection. Furthermore, this work also demonstrated that the decay of proviral HIV-DNA is similar to the decay of cell infectivity assessed by terminal dilution co-culture. In conjunction, one could hypothesize that a reduction of the latent reservoir indeed could translate into lowered viral setpoints and subsequent delay of disease progression. For this reason, proviral DNA as a valuable surrogate marker of the long lived cellular reservoir and potentially of the viral setpoint needs to be revisited in the context of primary HIV-infection. Furthermore, potentially other viral markers such as different HIV-RNA species [21-28] may be of additional value. A recent observational study suggested that early-cART treated PHI patients exhibited lower viral setpoints after stop of early-cART compared to controls when adjusted for baseline CD4 counts. Interestingly the CD4 count benefit observed, persisted for up to 72 weeks [9]. Another very recent study reported that a median duration of HAART of 1.1 years was associated with a persistent effect on viral load and CD4-T-cell count for up to 5 years after seroconversion [14]. In contrast to these results a short term treatment of 24 weeks did not show any benefit on viral setpoint and CD4 count [13]. In the near future, we mainly depend on observational studies because randomized clinical trials in this setting are not feasible [5].

Viral and host factors influence the HIV-1 viral setpoint

HIV infection is characterized by continuous viral replication at a high rate, which combined with the error rate of the reverse transcriptase [29, 30], frequent recombination [31, 32], and host selection pressure leads to a high genetic diversity in infected individuals [33-37]. However, the level of diversity between individual patients can vary considerably [36, 38-40]. After primary HIV infection each individual reaches a steady state level of plasma viral load which is referred to as viral setpoint. These setpoints between individuals can vary more than 1000 fold [41]. The switch in

coreceptor usage from CCR5 to CXCR4, which occurs in approximately 50% of patients, is associated with more vigorous viral replication *in vivo* exemplified by an increase in plasma viremia levels in HIV-infected individuals and more rapid disease progression [41-46]. Various viral and host properties may contribute to the observed diversity: these include differences in virulence, subtype, immunogenicity and replication capacity of the transmitted viruses, the quasispecies composition of the infecting inoculum (transmission of single versus multiple quasispecies), host genetic factors such as chemokine receptor polymorphisms, HLA types and gender differences [47-51]. HIV-specific CD4 and CD8 responses also contribute to control of viremia, however, optimal measurements for functional HIV-1 specific CD8 responses in humans have still to be determined. In particular, various recent studies in humans [10, 52-54] in contrast to earlier ones [55] were not able to link levels of HIV-specific CD8 responses with the viral setpoint. Neutralizing antibodies arising within weeks to months after PHI are also thought to contribute to the viral setpoint. Evidence, however, is mostly indirect by escape of neutralization responses and viral evolution of the *env* gene most likely driven by neutralizing antibodies directed against *env* [35, 37, 56]. Recently, we have shown that higher neutralizing antibody titers against autologous viruses indeed did correlate with viral setpoint reached in patients undergoing structured treatment interruptions [38]. More convincingly, first direct evidence for neutralizing activity *in vivo* was demonstrated by our passive immunization study, where a cocktail of three broadly neutralizing antibodies was administered to patients with suppressed viremia. Upon stop of cART, viral rebound could be delayed significantly, demonstrating that neutralizing antibodies indeed can have a direct effect on viral replication *in vivo* [57, 58] [59].

In addition to viral factors and immune responses it has been well described, that a variety of host genetic factors are influencing HIV-1 disease progression in a negative or positive way. Polymorphisms at the following genotypic locations have been found to influence disease progression: CCR5 delta 32, CCR5 G-2455A, CCR2 V64I, RANTES G-403A, RANTES C-28G, MIP-1a T113C, SDF-1 3'A. Moreover, a variety of HLA alleles have been found to accelerate AIDS (HLA-A, B, C homozygosity [60, 61], HLA-B*35 [62, 63], HLA-A*01-B*08-DRB1*03 [64, 65] and others have been demonstrated to delay disease progression such as HLA-B*57 and HLA*B27 [66]. Of interest one HLA association was even shown to correlate with maintenance of viral suppression in patients treated early after seroconversion; HLA-DRB1*13-DQB*6 [67]. Recently, a whole genome association study of major determinants for host control revealed three new relevant polymorphisms which can explain approx. 15% of the variation among viral setpoints in untreated asymptomatic patients [68]. For these reasons, it is evident that predictors of the viral setpoint cannot be studied anymore without also assessing these important factors – at least in part - in modulating the course of HIV-1 disease. Nevertheless, it has been shown many times that effects of these host genetic traits are subtle within single individuals and large patient cohorts are normally needed to demonstrate such effects. Thus, for our project we do not focus exclusively on host genetics, but rather will perform these analysis to exclude a potential bias as we have done so before [24, 69].

Taken together, prerequisites to comprehensively study viral and host factors are well defined patient groups that are followed longitudinally.

Current status of treatment interruptions in HIV-infected patients.

Originally, structured treatment interruptions were studied systematically for three reasons: Firstly, to test the autovaccination hypothesis, secondly, to reduce toxicity, and thirdly, to reduce exposure to antiretroviral drugs and therefore reduce costs. The autovaccination hypothesis has been rejected in chronically infected as well as in patients infected during primary HIV infection, meaning that short term-treatment interruptions, despite the fact that they could induce HIV-specific T-helper, - cytotoxic CD8 and humoral immune responses were not able to sustainably lower viral setpoints [10, 53, 54, 70-72]. CD4-guided treatment interruptions in lower CD4 strata were associated with increased frequencies of HIV-, non-HIV-related morbidity and non-HIV related mortality in two

large trials [73, 74]. However, increased morbidity and mortality were not seen in higher CD4-strata [75-77]. No data of structured treatment interruptions in large clinical trials performed in patients with primary HIV-infections are available to date. However, the fact that morbidity and mortality seen in the large trials were dependent at least in part on the CD4 stratum in which the cycling took place suggests that the risk for interruption of early ART introduced during PHI is minimal because patients with early-cART in most cases do reach normal or almost normal CD4 counts within the first year of treatment. Thus, taken together, the risk of harming patients who stop early PHI treatment is not existent or very low, given that high CD4 counts are reached after early PHI treatment, and that negative treatment interruption effects seen in chronic HIV-infection were very rare in general and CD4-dependent at least to some extent.

Current status of the Zurich PHV infection cohort

The Zurich PHI study has already been started at the beginning of 2002. First, patients were enrolled in the Merck study 520, Protocol No 013-00 (EK 851). At that timepoint we have already applied for a study extension in addition to the Merck protocol and this was accepted under the EK 851 and later on 1086). From our own research initiative, several manuscripts have already been published over the last 3 years:

1. Trkola A, Kuster H, Rusert P, Joos B, Fischer M, Leemann C, Manrique A, Huber M, Rehr M, Oxenius A, Weber R, Stiegler G, Vcelar B, Katinger H, Aceto L, Günthard HF. Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies. *Nature Medicine*. 2005;11:615-622.
2. Rusert P, Kuster H, Joos B, Misselwitz B, Gujer C, Leemann C, Fischer M, Stiegler G, Katinger H, Olson WC, Weber R, Aceto L, Günthard HF, Trkola A. Virus isolates during acute and chronic Human Immunodeficiency Virus Type 1 infection show distinct patterns of sensitivity to entry inhibitors. *Journal of Virology*. 2005;79:8454-8469.
3. Aceto L, Karrer U, Grube C, Oberholzer R, Hasse B, Presterl E, Böni J, Kuster H, Trkola A, Weber R, Günthard HF. Die Akute HIV Infektion in Zürich: 2002 – 2004. [Primary HIV-1 Infection in Zurich: 2002-2004] *PRAXIS (Schweizerische Rundschau für Medizin)* 2005;94:1199-1205.
4. Joos B, Trkola A, Aceto L, Fischer M, Vcelar B, Stiegler G, Katinger H, Kuster H, Günthard HF. Multiple dose pharmacokinetics of combined anti-HIV-1 human monoclonal antibodies 2G12, 4E10 and 2F5 administered intravenously to HIV-infected patients. *Antimicrobial Agents and Chemotherapy*. 2006;50:1773-1779.
5. Huber M, Fischer M, Misselwitz B, Manrique A, Kuster H, Niederöst B, Von Wyl V, Weber R, Günthard HF and Trkola A. Antibody and complement mediated lysis activity contributes to viremia control in the acute phase of HIV-1 infection. *PLOS Medicine* 2006; 2006;3:2078-2093. (e441)
6. Manrique A, Rusert P, Joos B, Fischer M, Kuster H, Leemann C, Niederöst B, Weber R, Stiegler G, Katinger H, Günthard HF, Trkola A. In vivo and in vitro escape from neutralizing antibodies 2G12, 2F5 and 4E10. *Journal of Virology* 2007;81:8793-8808.

This study so far has been highly successful and for this reason it was decided to continue with our own protocol after Merck has stopped to enrol patients. To date we have enrolled more than 140 patients with documented primary HIV infection within the first 5 years. An interim analysis of 62 patients [78] focusing on clinical aspects like delay to diagnose HIV on first physician contact due to difficulty to recognize the “acute retroviral syndrome” (ARS), symptoms and signs, laboratory abnormalities, primary resistance and mode of transmission revealed that clinical characteristics of the Zurich PHI cohort are comparable with other published PHI studies [79-81]. Approximately 90% of patients so far have chosen to undergo early-cART. To this end 50 patients have stopped antiretroviral treatment. Primary resistance has only been detected in 4% so far and approx. 70% were infected with a subtype B strain. Criteria for diagnosis of PHI are: 1) acute retroviral syndrome [78] and negative or indeterminate westernblot in the presence of a positive p24Ag and/or detectable plasma HIV-1 RNA. 2) documented seroconversion with or without symptoms within 90 (acute infection) or 180 days (recent infection). 3) possible ARS, positive westernblot and detectable HIV-RNA, and a negative HIV-gp120 avidity assay [82, 83] or a detuned assay [84] (recent infection). Overall, 73 patients (63%) had a negative or indeterminate westernblot, respectively 97 patients could unambiguously be identified to be acutely infected. Thus, the Zurich PHI cohort is well characterized and suitable for the work proposed here.

3. Study objectives

Primary study objectives:

- To enrol and longitudinally follow patients with documented primary HIV infection referred to the Division of Infectious Diseases, University Hospital Zurich. (either defined as acute or recent infection).

Secondary study objectives:

- To evaluate the effect of early-cART on the viral setpoint
- To determine viral factors, potentially relevant for HIV-1 pathogenesis: a) Transmission of drug resistance, b) cellular levels of proviral DNA, c) levels of different cell associated HIV-RNA species, d) viral diversity, e) replication capacity, f) isolation of replication competent virus
- To determine HIV specific immune responses: a) kinetics of anti-HIV-1 specific humoral immune responses, b) kinetics of HIV-specific cellular immune responses, c) investigation of factors associated with the innate immune system.
- To determine genetic traits known to be associated with differential progression in natural HIV-infection, such as (HLA typing, chemokine receptor polymorphisms, cellular factors, potentially new genes of interest).
- To search for viral and immunological factors which are associated with HIV-1 transmission.

4. Patient population

As per 30 July 2007 148 patients were enrolled under the former protocols approved by the Ethics committee (No. EK 852 and EK 1086). All patients enrolled previously will be asked to sign the informed consent of the current project (INFZ-ZPHI 01.01, Version 1) retrospectively. We expect to enroll another 150 patients by the end of 2011. This is a realistic scenario assuming the same rate of new HIV-1 infections as we have observed over the last 5 years.

Patient enrollment:

Patients with documented primary HIV-1 infection who agree to participate in the current study will receive the following routine screening at baseline: total blood count, routine chemistry laboratory (e.g. creatinine, liver enzymes, lipid profile, c-reactive protein, serum-glucose), HIV-1 RNA, p24Ag, HIV-genotypic drug resistance test, Western-blot, (HIV-screening if still necessary), CD4 count, and further laboratory testing belonging to the standard procedure for patients presenting with new HIV-infection (Hepatitis, A, B, C serologies, CMV-, syphilis-, toxoplasmosis- serologies etc.). All these tests are covered by regular health insurance because they reflect standard of care.

Inclusion Criteria:

- Patients of 18 or more years who present with a documented primary HIV-infection defined as:

A) **acute HIV-1 infection**, defined as:

- acute retroviral syndrome [78] (ARS) and negative or indeterminate Westernblot in the presence of a positive p24 Ag and/or detectable plasma HIV-1 RNA
- documented seroconversion with or without symptoms within 90 days.

or

B) **recent HIV-1 infection**, defined as:

- possible ARS, positive Westernblot and detectable HIV-RNA, and a negative HIV-gp120 avidity [82, 83], respectively detuned assay [84].
- documented acute HIV-1 infection, however, referral to our center more than 90 days after presumed date of infection.

Exclusion criteria:

- Hemoglobin < 10 g/dl (men) and < 9 g/dl (women) at the time of enrollment.

5. Study site

This is an open label, non-randomized monocenter, observational study, conducted at the

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Rämistrasse 100
8091 Zürich

6. Intervention

Patients with intervention:

Intervention a):

Early combined antiretroviral treatment (early-cART): All patients with documented acute HIV-1 infection, presenting within 90 days after presentation of ARS or documented seroconversion will be offered early combination antiretroviral treatment with a standard firstline cART regimen as recommended in treatment guidelines [85] containing drugs that are approved by Swissmedic. Treatment will be continued until at least 12 months complete HIV-RNA suppression in the plasma has been achieved (HIV-plasma RNA < 50 copies/ml for at least 12 months (see Figure 1).

Intervention b):

Interruption of early-cART: After one year of fully suppressive early-cART patients can stop cART and then will be switched to the observational study arm (see Figure 1).

Patients without intervention:

All patients with documented acute HIV-1 infection who do not want to have early-cART, respectively patients with documented recent infection will be enrolled in the observational study group only (see Figure 1).

7. Drug regimes selected for early-cART

Initial treatment consists of a ritonavir-boosted protease inhibitor (PI) combined with two nucleoside reverse transcriptase inhibitors (nRTI) (e.g. lopinavir/ritonavir: 2 x per day 200/50 mg in combination with zidovudin/lamivudin: 2 x per day, 300/150 mg). This is a well established, potent

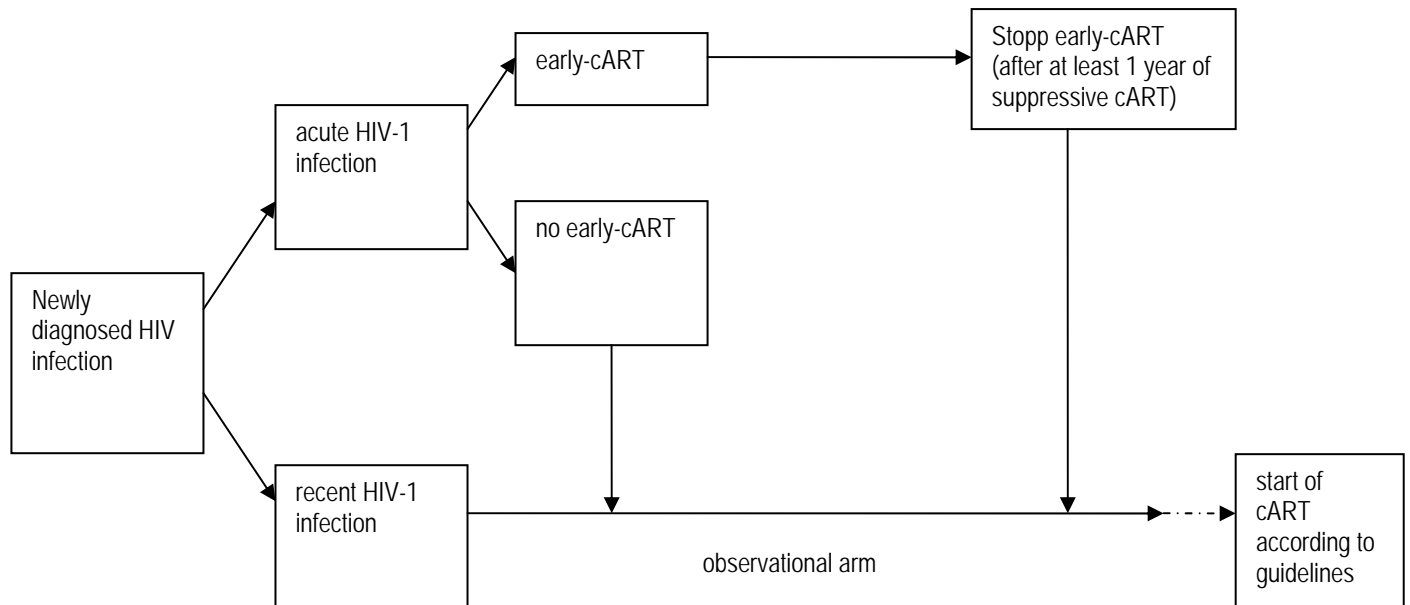
drug combination with excellent efficacy as a first line treatment. This treatment is chosen because the boosted protease inhibitor has a high genetic barrier, which is particularly important because NNRTI resistance mutations transmitted, may hamper the whole NNRTI based first line treatment from the beginning (von Wyl et al, Archives of Internal Medicine, 2007, in press). If side effects or toxicity do arise, respectively results from the resistance test recommends a different drug regimen, different early-cART regimens are chosen. In this case the following alternative boosted-PI regimens will be chosen (atazanavir/ritonavir: once daily 300/100 mg, darunavir/ritonavir: 2 x per day 600mg/100mg). If a boosted-PI regimen is not possible, a non-nucleoside-reverse-transcriptase inhibitor (NNRTI) based regimen (e.g. efavirenz: once daily 600mg or nevirapin: 200mg 2 x per day, or once daily 400mg) is also possible. As alternative NRTI regimens, abacavir and lamivudin: once daily 600/300mg, or tenofovir and emtricitabin: once daily 300mg/200mg will be used.

8. Safety of cART

Safety of cART will be monitored the same way as this is done in clinical routine: week 2, 4, 8, 12 and thereafter every three months. In women who undergo early-cART and are pregnant a drug regimen will be chosen, which excludes efavirenz.

9. Study flow chart

a) The diagram below shows a schematic outline of the study:



b) Under **Appendix I, III, III** sequential blood drawing is shown schematically in three tables:

Appendix I (page 15-16): This table depicts patient visits and planned amounts of blood that will be drawn from patients who will undergo early-cART. Furthermore, in the right column a synopsis of the total amount of blood per timepoint (blood for clinical routine purposes and study blood) is shown.

Appendix II (page 17-18): This table shows patient visits and planned amounts of blood that will be drawn from patients who will interrupt their early-cART treatment after at least one year of successful suppression (plasma HIV-RNA <50 RNA copies/ml for at least 12 months). Furthermore, in the right column a synopsis of the total amount of blood per timepoint (blood for clinical routine purposes and study blood) is shown.

Appendix III (page 19-20): This table shows patient visits and planned amounts of blood that will be drawn from patients who have not chosen to start early-cART treatment or who have presented with “recent infection”. Furthermore, in the right column a synopsis of the total amount of blood per timepoint (blood for clinical routine purposes and study blood) is shown.

c) *Specimen Collection and Processing*

Blood specimens will be obtained according to the tables of appendix I – III.

EDTA-Blood from all time points will be separated into cells and plasma according to standard procedures. Cellular material is divided into aliquots that are stored either in DMSO medium in liquid nitrogen to yield viable cells for immunological analysis, or stored at -70°C as dry cell

pellets to provide material for genetic analysis and viral load measurements. All plasma samples are stored at -70°C .

11. Endpoints and statistical analysis

Analysis of the parameters described under secondary study objectives will be performed upon availability of data. Exact description of these research projects are not feasible within this study protocol. Briefly, the following analyses are planned:

- Viral setpoints of patients having stopped early-cART will be compared with viral setpoints from patients with primary HIV infection without early-cART and with viral setpoints from patients with documented time of seroconversion enrolled in the Swiss HIV cohort study (historic controls). A first interim analysis will be performed in 2009.
- Moreover, the cART free interval between patients undergoing early-cART (from timepoint of stopping their first cART to timepoint of initiation of second cART according to current guidelines) and patients without early-cART (timepoint of initiation of cART according to current guidelines) will be determined.
- In addition, analysis of parameters described under secondary study objectives will be performed after the research data has been generated. In general, these parameters will be measured longitudinally, and kinetics of these parameters will be determined and compared between groups with and without early-cART.

Standard statistical methods will be used for these analyses. Details of the planned analyses have been described in Swiss National Science Foundation research proposals:

“Humoral immunity to HIV-1: Analysis of the function of antibody responses as correlate and surrogate marker of viremia control”, SNF Nr. 3100A0-103748 *“Factors associated with viral control after primary HIV-1 infection and viral determinants associated with HIV-1 transmission.”*, SNF No. 324700-116035 (Principle Investigator: H. Günthard).

12. Time frame

The current study is the successor of two previous studies: Merck study 520 (EK 851) and the extension of that study (EK 1086). Patient enrollment for these two studies has been conducted between January 2002 – End of August 2007.

We will enroll patients under this new protocol as soon as it is accepted by the ethics committee. We expect to enroll patients from September 2007 – end of 2011. Laboratory investigations and the observational period will continue until 2016.

13. Laboratory investigations

a) **“Standard of Care” clinical laboratory investigations:** Laboratory investigations in the context of clinical care will be carried out by the various diagnostic laboratories of the University Hospital and the University of Zurich.

b) **“Research laboratory investigations”:** Isolation of autologous virus, humoral immune responses including neutralizing antibody escapes, antibody dependent cellular cytotoxicity (ADCC), innate immune responses, (complement lysis, natural killer cell activity), isolation and

studies of B-Zell function, determination of proviral DNA and of different HIV-RNA species, determination of viral diversity, envelope sequencing and viral replication capacity assays will all be performed in the HIV research laboratory of the Division of Infectious Diseases and Hospital Epidemiology in collaboration with Prof. Dr. A. Trkola and PD Dr. M. Fischer.

The following laboratory research will be conducted in collaboration with:

- HIV-specific cellular immune responses (Prof. A. Oxenius, ETH Zurich)
- Determination of HIV-drug resistant minority quasispecies (PD Dr. K. Metzner, University of Erlangen).

14. Ethics and Trial registration

Informed consent.

Informed consent from each subject participating in the trial will be obtained before any trial specific procedures are performed on the subject. The aims, methods, benefits, and potential hazards of the trial will be explained to each participant before signing the informed consent.

It will be made clear that each subject can withdraw their consent at any time and for any reason, without incurring any penalty or withholding of treatment on the part of the investigator.

Signed informed consent forms will be kept on file by the investigator and a copy of it will be given to the patient upon request.

Patients who have already been enrolled in the EK protocol No 851 and 1086 will be consented again under this new protocol.

This trial will be registered in the trial registry of the University Hospital Zurich and in the international trial registry “clinical.trials.gov” (www.clinical.trials.gov).

15. Safety features and insurance

Safety evaluations.

- Vital signs will be monitored at baseline (body temperature, pulse and blood pressure).
- Physical examination will be performed at baseline and later on if needed.
- Complete Blood Count (CBC) including white blood cell differential, and platelet count: at baseline
- Chemistry including AST, ALT, bilirubin, creatinin, at baseline
- Urine analysis (Uristix and sediment): at baseline and later on if needed.
- CD4 count: at baseline
- HIV-plasma RNA: at baseline
- genotypic HIV drug resistance testing: at baseline

For patients who will undergo early antiretroviral treatment safety laboratory (chemistry and CBC will be repeated at week 2, 4, 8, 12 and then every three months thereafter.

Viral load and CD4 monitoring occurs monthly until VL is undetectable and thereafter every three months.

For patients not undergoing early-cART, plasma HIV-RNA and CD4 count will be repeated every 3 months and CBC and chemistry will be repeated every 6 months as it is done in standard clinical care.

If the study participants encounter damage caused by the present study, such damage is covered by the insurance policy of the University Hospital Zurich.

16. Feasibility

The fact that 148 patients have already been recruited (January 1, 2002 - July 30, 2007) under the previous protocols (EK 851 and EK 1086) demonstrates that the study is feasible. The infrastructure and know-how in the clinic and research laboratories is in place. Thus, the capacity to conduct the study is available. Furthermore, all collaborations are working and fully active.

17. Finances

The current study is sponsored by the Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich. Research expenses are covered by a variety of project specific separate research grants (Swiss National Science Foundation and private foundations).

18. Investigators

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Co-Investigator:

Prof. Dr. med. Rainer Weber

Both at the University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Zurich, Switzerland

19. Publications

If, at the end or during the trial, publications or presentations of the results of this trial are planned then all parties involved in the respective research work have the right to review the manuscript and abstracts before their submission. However, decision for submission of a manuscript or abstract is made by the principal investigator.

Zürich, 7 August 2007

Principal Investigator

Prof. Dr. med. H. Günthard

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Zürich PHI - Studie (INFZ-ZPHI-01) - Synopsis Blutentnahmen für Patienten mit Frühtherapie

SHCS Nr.

geb. Datum

Initialen

Name

Vorname

Datum	Studien Phase	Visiten Nr.	Woche	Visiten	Routine Labor	Blutabnahme		Blutmenge ml	Blutmenge ml	Blutmenge ml	Synopsis der Blutmenge geordnet nach Studienphasen	
				Zürich	usz	Zürich EDTA 10ml	Total/ ACD 10ml	Studie	Routine	Total		ml
					AKI,NZR							
	Screening * (1. Visite)	0	minus x	x	(RES,VL,CD4) (Häm, Chemie) (W-Blot, p24)	4	4	64	60	124	Total Blutmenge in 3 Monaten	444
.....	Studieneintritt*	1	0	x	CD4/RNA	10	0	80	20	100		
.....	Induktionsphase	2	4	x	RNA	4	0	32	20	52		
.....	Induktionsphase	3	8	x	CD4/RNA	8	0	64	20	84		
.....	Induktionsphase	4	12	x	CD4/RNA	8	0	64	20	84		
.....	Beobachtungsph.	5	16	x	CD4/RNA	5	0	40	20	60	Total Blutmenge in 9 Monate	368
.....	Beobachtungsph.	6	24	x	CD4/RNA	7	0	56	20	76		
.....	Beobachtungsph.	7	32	x	CD4/RNA	5	0	40	32	72		
.....	Beobachtungsph.	8	40	x	CD4/RNA	5	0	40	20	60		
.....	Beobachtungsph	9 (Ende Jahr 1)	48	x	CD4/RNA	10	0	80	20	100		
.....	Beobachtungsph.	10	68	x	CD4/RNA	5	0	40	32	72	Total Blutmenge Jahr 2	244
.....	Beobachtungsph.	11	84	x	CD4/RNA	5	0	40	20	60		
.....	Beobachtungsph.	12 (Ende Jahr 2)	100	x	CD4/RNA	8	0	64	48	112		

				Visiten	Routine Labor	Blutabnahme Anzahl Röhrchen		Blutmenge ml	Blutmenge ml	Blutmenge ml	Synopsis der Blutmenge geordnet nach Studienphasen	
Datum	Studien Phase	Visiten Nr.	Woche	Zürich	usz	Zürich EDTA 10ml	Total/ ACD 10ml	Studie	Routine	Total		
					AKI,NZR	für Fried.	Herbert					
.....	Beobachtungsph.	13	116	x	CD4/RNA	5	0	40	28	68	Tot. Blutmenge Jahr 3	300
.....	Beobachtungsph.	14	132	x	CD4/RNA	5	0	40	20	60		
.....	Beobachtungsph.	15	148	x	CD4/RNA	5	0	40	48	88		
.....	Beobachtungsph.	16 (Ende Jahr 3)	164	x	CD4/RNA	8	0	64	20	84		
.....	Beobachtungsph.	17	180	x	CD4/RNA	5	0	40	32	72	Total Blutmenge Jahr 4	244
.....	Beobachtungsph.	18	196	x	CD4/RNA	5	0	40	20	60		
.....	Beobachtungsph.	19 (Ende Jahr 4)	212	x	CD4/RNA	8	0	64	48	112		
.....	Beobachtungsph.	20	228	x	CD4/RNA	5	0	40	32	72	Total Blutmenge Jahr 5	244
.....	Beobachtungsph.	21	244	x	CD4/RNA	5	0	40	20	60		
.....	Beobachtungsph.	22 (Ende Jahr 5)	260	x	CD4/RNA	8	0	64	48	112		

Blutvolumen für verschiedene Routine Blutentnahmen:

HIV RNA: 6ml, CD4 Zellen: 3 ml, Blutbild: 3 ml, Routine - Chemie: 3 ml, Serothek HIV Kohortenstudie: 12 ml, Zytothek HIV Kohortenstudie: 16 ml

HIV-Resistenztest: 10 ml, Westerblot: 8 ml, p24 Ag: 8 ml

*** Visite bevor antiretrovirale Therapie begonnen wird**

(Resistenz, SHCS, andere baseline Laboruntersuchungen (Chemie, Hämat, Serologien etc))

Falls Diagnose schon klar ist von auswärts her, kann Screening Visite und Studieneintritts-Visite zusammengefasst werden (dann 10 EDTA für Friederike und 4 ACD für Herbert)

Zürich PHI - Studie (INFZ-ZPHI-01) - Synopsis Blutentnahmen nach Stop der Frühtherapie

SHCS Nr.	geb. Datum	Initialen
Name	Vorname	

Datum	Studien Phase	Visiten Nr.	Monat	Woche	Visiten	Routine Labor	Blutmenge Anzahl Röhrchen	Blutmenge ml	Blutmenge ml	Blutmenge ml	Synopsis der Blutmenge geordnet nach Studienphasen ml	
					Zürich	USZ	Zürich EDTA 10ml	Studie	Routine	Total		
	für wen					AKI	für F. Burgener					
.....	stop ART	0	0	0	x	(VL,CD4)	10	80	20	100	Total Blutmenge für 1. Jahr Nachbeobachtungszeit	640
.....	Nachbeob-Phase	1		2	wiss	0	3	24	0	24		
.....	Nachbeob-Phase	2	1	4	x	(VL)	5	40	0	40		
.....	Nachbeob-Phase	3		6	wiss	0	3	24	0	24		
.....	Nachbeob-Phase	4	2	8	x	(VL, CD4)	10	80	0	80		
.....	Nachbeob-Phase	5	3	12	x	(VL)	3	24	20	44		
.....	Nachbeob-Phase	6	4	16	x	(VL,CD4)	10	80	0	80		
.....	Nachbeob-Phase	7	5	20	x	(VL)	3	24	0	24		
.....	Nachbeob-Phase	8	6	24	wiss	0	5	40	32	72		
.....	Nachbeob-Phase	9	7	28	x	(VL,CD4)	3	24	0	24		
.....	Nachbeob-Phase	10	9	36	x	(VL,CD4)	5	40	0	40		
.....	Nachbeob-Phase	11	12	52	x	(VL,CD4)	5	40	48	88		

Datum	Studien Phase	Visiten Nr.	Monat	Woche	Visiten	Routine Labor	Blutmenge Anzahl Röhrchen	Blutmenge ml	Blutmenge ml	Blutmenge ml	Synopsis der Blutmenge geordnet nach Studienphasen	
					Zürich	USZ	Zürich EDTA 10ml	Studie	Routine	Total	ml	
						AKI	für F. Burgener					
.....	Nachbeob-Phase	12	16	64	x	(VL,CD4)	3	24	0	24	Total Blutmenge für 2. Jahr	208
.....	Nachbeob-Phase	13	19	76	x	(VL,CD4)	5	40	32	72		
.....	Nachbeob-Phase	14	22	88	x	(VL,CD4)	3	24	0	24		
.....	Nachbeob-Phase	15	25	100	x	(VL,CD4)	5	40	48	88		
.....	Nachbeob-Phase	16	28	112	x	(VL,CD4)	3	24	0	24	Total Blutmenge für 3. Jahr	208
.....	Nachbeob-Phase	17	31	124	x	(VL,CD4)	5	40	32	72		
.....	Nachbeob-Phase	18	34	136	x	(VL,CD4)	3	24	0	24		
.....	Nachbeob-Phase	19	37	148	x	(VL,CD4)	5	40	48	88		
.....	Nachbeob-Phase	20	40	160	x	(VL,CD4)	3	24	0	24	Total Blutmenge für 4. Jahr	208
.....	Nachbeob-Phase	21	43	172	x	(VL,CD4)	5	40	32	72		
.....	Nachbeob-Phase	22	46	184	x	(VL,CD4)	3	24	0	24		
.....	Nachbeob-Phase	23	49	196	x	(VL,CD4)	5	40	48	88		
.....	Nachbeob-Phase	24	52	208	x	(VL,CD4)	3	24	0	24	Total Blutmenge für 5. Jahr	248
.....	Nachbeob-Phase	25	55	220	x	(VL,CD4)	5	40	0	40		
.....	Nachbeob-Phase	26	58	232	x	(VL,CD4)	3	24	32	56		
.....	Nachbeob-Phase	27	61	244	x	(VL,CD4)	5	40	0	40		
.....	Nachbeob-Phase	28	64	256	x	(VL,CD4)	5	40	48	88		

Zürich PHI - Studie (INFZ-ZPHI-01) - Synopsis Blutentnahmen Primo-Studie ohne Früh-Therapie

SHCS Nr.

geb. Datum

Initialen

Name

Vorname

Datum	Studien Phase	Visiten Nr.	Monat	Woche	Visiten	Routine Labor	Blutmenge Anzahl Röhrchen		Blutmenge ml	Blutmenge ml	Blutmenge ml	Synopsis der Blutmenge geordnet nach Studienphasen	
					Zürich	USZ	Zürich EDTA 10ml	Zürich ACD 10ml	Studie	Routine	Total		ml
	für wen					AKI,NZR	für F. Burgener	Herbert					
	Screening	0	0	minus x	x	(RES,VL,CD4) (Häm, Chemie) (W-Blot, p24)	4	4	64	60	124	Total Blutmenge für 1. Jahr Studie ohne Therapie	636
.....	Eintritt in Studie	1	0	0	x	(VL, CD4)	10	0	80	20	100		
.....	keine Therapie	2		2	x	(VL)	3	0	24	0	24		
.....	keine Therapie	3	1	4	x	(VL, CD4)	5	0	40	0	40		
.....	keine Therapie	4		6	wiss	0	3	0	24	0	24		
.....	keine Therapie	5	2	8	x	(VL, CD4)	10	0	80	0	80		
.....	keine Therapie	6	3	12	x	(VL, CD4)	3	0	24	20	44		
.....	keine Therapie	7	6	24	x	(VL, CD4)	10	0	40	32	72		
.....	keine Therapie	8	9	36	x	(VL,CD4)	5	0	40	0	40		
.....	keine Therapie	9	12	52	x	(VL,CD4)	10	0	40	48	88		
.....	keine Therapie	10	16	64	x	(VL,CD4)	3	0	24	0	24	Total Blutmenge für 2. Jahr	208
.....	keine Therapie	11	19	76	x	(VL,CD4)	5	0	40	32	72		
.....	keine Therapie	12	22	88	x	(VL,CD4)	3	0	24	0	24		
.....	keine Therapie	13	25	100	x	(VL,CD4)	5	0	40	48	88		

					Visiten	Routine Labor	Blutmenge Anzahl Röhrchen		Blutmenge ml	Blutmenge ml	Blutmenge ml	Synopsis der Blutmenge geordnet nach Studienphasen	
Datum	Studien Phase	Visiten Nr.	Monat	Woche	Zürich	USZ	Zürich EDTA 10ml	Zürich ACD 10ml	Studie	Routine	Total		ml
	für wen					AKI,NZR	für F. Burgener	Herbert					
.....	keine Therapie	14	28	112	x	(VL,CD4)	3	0	24	0	24	Total Blutmenge für 3. Jahr	208
.....	keine Therapie	15	31	124	x	(VL,CD4)	5	0	40	32	72		
.....	keine Therapie	16	34	136	x	(VL,CD4)	3	0	24	0	24		
.....	keine Therapie	17	37	148	x	(VL,CD4)	5	0	40	48	88		
.....	keine Therapie	18	40	160	x	(VL,CD4)	3	0	24	0	24	Total Blutmenge für 4. Jahr	208
.....	keine Therapie	19	43	172	x	(VL,CD4)	5	0	40	32	72		
.....	keine Therapie	20	46	184	x	(VL,CD4)	3	0	24	0	24		
.....	keine Therapie	21	49	196	x	(VL,CD4)	5	0	40	48	88		
.....	keine Therapie	22	52	208	x	(VL,CD4)	3	0	24	0	24	Total Blutmenge für 5. Jahr	248
.....	keine Therapie	23	55	220	x	(VL,CD4)	5	0	40	0	40		
.....	keine Therapie	24	58	232	x	(VL,CD4)	3	0	24	32	56		
.....	keine Therapie	25	61	244	x	(VL,CD4)	5	0	40	0	40		
.....	keine Therapie	26	64	256	x	(VL,CD4)	5	0	40	48	88		