HIV Care in Times of COVID-19 – Rapid Treatment Start Seems as Vital and Cost-Effective Approach in Central and Eastern Europe

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Abstract

Background:

In times of SARS-CoV-2 epidemic it is essential to deliver specialist HIV care with a maximum effectiveness, but minimum epidemiological risk. Therefore, we aimed to determine whether rapid linkage to care defined as starting combined antiretroviral therapy (cART) at the day of first visit in HIV clinic is a cost-effective approach.

Methods:

The analysis used Markov's lifetime model presented in our previous study. The input data used in the model were updated in terms of costs, life expectancy tables and patient's characteristics. This analysis used information from the previous model about the additional cost of treatment and QALY lost in the life horizon for people newly infected with HIV. Number of new infected persons was estimated on the basis of available data.

Results:

Input data were available for 344 MSM patients who registered in HIV specialist care between 2016 and 2017. Estimated QALY loss due to no rapid treatment in case of no taking (taking) into account viral load equal 0.018 (0.022), 0.039 (0.047), 0.131 (0.158) respectively in low, medium and high-risk transmission groups. Rapid cART initiation was dominant regardless of the chosen scenarios.

Conclusions:

Taking into account HIV transmission in cost-effectiveness analysis indicates that rapid-initiation of HIV treatment is profitable.

Background

The sustainability of already achieved progress in stopping HIV, defined by 90-90-90 WHO goal, may be endangered in times of SARS-CoV-2 epidemic.¹ In addition the responsibilities of clinical centres expanded as it is essential to deliver specialist HIV care with maximum effectiveness, but minimum epidemiological risk. Although HIV infection itself is not considered as higher risk of SARS-CoV-2 infection or more severe COVID-19, people living with HIV have many co-morbidities that pose such risk.^{2,3} In addition it cannot be excluded that HIV-positive people who are not yet on treatment and those with low CD4+ count may be at increased risk of COVID-19.² Therefore patients would additionally benefit from limiting number of contacts with other patients and healthcare providers. Rapid treatment start presents such advantage through limiting number of visits and contacts. In addition rapid start proved to be effective method of linkage to care and is recommended by the IAS-USA, in recognition of many structural barriers that may prevent people to be immediately linked to care.⁴

HIV care in times of SARS-CoV-2 pandemic faced new challenges and needs. European region was disproportionately affected by the epidemic. In Central and Eastern Europe half of physicians involved in HIV care was at the same time involved in COVID-19 treatment.⁵ Therefore rapid treatment start, defined as starting therapy on the first clinical visit and prior to obtaining test results seems as vital option. Here we aimed to determine whether starting combined antiretroviral therapy (rapid cART) at the first visit in HIV clinic is a cost-effective approach for this region of Europe.

Methods

Our analyses were performed to assess the potential benefits and costs in the population of men having sex with men (MSM) related to immediate starting treatment at the time of HIV diagnosis compared to standard treatment path.

For this paper a new simple computational model was built to assess the cost-effectiveness of rapid cART treatment for newly diagnosed HIV infected patients, from the public payer's perspective. Due to the analyzed disease and compared treatment paths, it was decided to take into account the effects and costs only in the period from diagnosis to start cART (possible gains resulting from earlier treatment at later time were omitted). Because of characteristics of HIV treatment and short period of delaying treatment, the presented simplification should not cause significant differences in patient's state of health and precisely illustrates the incremental effect of compared paths of treatment (Figure 1). The above assumption in case of previously published papers suggesting that delaying to cART is associated with additional costs, could be considered as a conservative approach.⁶

In our calculations, we also used the lifetime Markov model built during previous study (Kowalska 2017), which allowed to perform cost-utility analysis and determinate quality-adjusted lost years of life and additional costs for the payer for newly HIV infected patients.⁶

The model has one-month cycles and takes into account 33 events or illnesses divided into 18 health states and 8 additional events or diseases affecting estimated costs and the length of life. The baseline state of the model is an asymptomatic HIV, that was the people with HIV who did not experience additional comorbidities. In each cycle of analysis, patients were distributed between health states with assigned corresponding probabilities. We made the assumption, that after changing baseline health state it was not possible for the person to change their health state, except for death incidence, there was no possibility of the occurrence of the same event repeatedly and no possibility of having several diseases at the same time (Figure 2). Detailed information about used Markov model was described in the previous study Kowalska 2017.⁶

For the purposes of this analysis, the previously developed Markov model were also updated in case of baseline characteristics of patients who registered in HIV specialist care between 1st January 2016 and 31st December 2017: mean CD4+ cells count, median HIV RNA and others (Table 1) and costs.

Risk of HIV transmission per sexual act

In the first stage, based on the unsystematic literature review, the number of potentially avoided new HIV infections were estimated due to rapid treatment implementation.

To find the necessary data on the risk of HIV transmission due to a sexual acts among MSMs, a research of the Medline medical database (via Pubmed) were performed. During the search, attempts were made to narrow down to the most reliable studies, i.e. meta-analysis that would be best suitable to our analysis population namely MSM patients not yet treated with cART. As part of the search, three publications were finally included to the analysis, Lasry 2014,⁷ Patel 2014⁸ and Baggaley 2018⁹ in which the risk of transmission per sexual act were found (Table 2). Due to the fact that the Baggaley 2018 study was published quite recently in 2018 and its significant extent of scope of study is also included in other reviews, it was decided to use this data in the base case scenario of analysis. In addition, the results from the remaining reviews were decided to be tested in a sensitivity analysis.

Time from diagnosis to start cART treatment

Based on the data collected for the MSM who registered in HIV specialist care, such as time of conducting the HIV-test, time of HIV diagnosis and the start of cART treatment, the average and median time of delay in access to therapy were determined. The statistical analysis of survival curves for the time to start treatment. was conducted. In the final calculations, curves based on the generalized gamma distribution (main scenario) and Weibull distribution (sensitivity analysis) were selected cause by the best fit according to the AIC and BIC criteria (Figure 3).

Viral load and risk transmission

Literature studies clearly show that plasma viral load is directly associated with risk of sexual transmission of HIV. Hence, the new simple computational model built for this analysis allows to perform calculations for two different variants: 1. Excluding impact of viral load at the risk of HIV transmission and 2. Including the level of viremia.

The baseline risk of HIV transmission adopted based on the data found in the review was adjusted for HIV RNA viral load according to the Quinn 2000¹⁰ study. In that paper, it was estimated that each log increase in viral load was associated with an increase by a factor of 2.45 in the risk of transmission.

In the first stage, the data for the cohort was stratified into five risk groups depending on the viral load levels, similarly to the Quinn 2000¹⁰ publication. Based on this data, the average level of HIV RNA viral load in each of the five groups was also determined. Finally, due to the small size of the group with level of viral load between 1.70 to 3.54 $\log_{10}$ HIV RNA copies/ml (only 11 patients from 344 patients from the cohort, 3%) it was decided to include them into group of patients under 3.54 $\log_{10}$ copies HIV RNA copies. Then, the probability of HIV transmission was determined for each group based on the difference between mean viral load in each group compared to the mean value on level of HIV viral load in the whole cohort and using data from the Quinn 2000 study.

For example, in the group of patients with 1.70- 3.54 $\log_{10}$ HIV RNA copies/ml, the average level of viremia was 2.77 $\log_{10}$ copies and was about 1.86 $\log_{10}$ copies/ml lower than the average level of viral load in the entire cohort. According to the data in the Quinn study, this difference is associated with more than 5-fold reduction risk of sexual transmission to 19% of the baseline risk from Baggaley 2018⁹ and others.

Ultimately, when impact of viral load at the risk of HIV transmission was included into our assesment , the propability of HIV transmission per insertive sexual act for patients with less than 3.54 $\log_{10}$ HIV RNA copies/ml was established at level 0.01% compared to 0.17% reported in the Baggaley 2018⁹ study. Detailed information about probabilities of new HIV infections per sexual act for all stratified groups was presented in Table 2.

Risk profiles of sexual behavior

In our analysis, HIV transmission was assumed to occur only through sexual contacts.

The probability of infection was based on data found in published meta-analyses. Our calculation also takes into account the impact of condom uses for final risk of transmission.

Due to the methodology of the analysis and showing the incremental effect of immediate starting treatment at the time of HIV diagnosis, the estimated number of new HIV infections relates to the period in which patient is not receiving cART. Profiles of the risk of transmission were adopted in a similar way as in the previous study Kowalska 2017⁶ i.e based on the average number of sexual partners, number of sexual acts, % frequency of condom use per act.

Additionally, we assumed that each patient from the analysed cohort had the same number of intercourses and had the same number of intercourses with each sexual partner. For the medium risk scenario, which was considered a baseline model, the rate of transmission was estimated assuming that an average HIV positive person has 10 partners per year, 10 monthly sex acts and 50% frequency of condom use per act. For the low and high-risk scenarios we assumed a person to have 3 and 50 partners per year, 10 and 20 sex acts per month and 90% and 0% coverage with condom use, respectively.

In our analysis also assumed that 28% of MSM patients have HIV+ partners (this assumption reduces the total number of new potential infections)⁶

Costs and other data

For the purposes of this analysis, previously Markov model was updated in terms of each health state representing different AIDS and Non-AIDS defining illness and the costs of cART treatment. The costs of cART treatment were adopted based on actual data from the National Program of cART Treatment and expert opinion, which was adopted at EUR 482 per month (461EUR drugs and 22 EUR monitoring treatment) while the cost of treating health states were adjusted based on inflation rate between 2015 and

2019 published by the Central Statistical Office.¹¹ Additionally, data about patient mortality used in Markov model, i.e. life expectancy tables was updated.

Additional costs related to the implementation of rapid cART were not included due to the method of financing of Centers of HIV Treatment in Poland as flat-fee. The simplification approach should not have a significant impact on inference from the analysis and results.

Results

Transmission risk with no adjustment for viral load level

In base case scenario (scenario A1), which include data from Baggaley 2018, the estimated avoided sexual HIV transmission rate within rapid cART therapy was from 0·011 to 0·076 compared to receiving cART immediately later. A lower transmission rate due rapid cART leads to additional QALY gained and savings costs of treatment associated with avoiding new infections. Estimated additional QALY gained due to avoid new HIV infections was from 0·018 to 0·131 depends on risk profile (low, medium and high). The additional costs savings of treatment associated with lack of new infections range from EUR745 for low risk profile to EUR 5 351 for high-risk profile.

Despite the additional costs of treatment since day of HIV diagnosis related to the implementation of rapid cART, this path were associated with savings for the public payer in the amount from EUR331 to EUR4 937 in lifetime horizon per 1 included patients.

Rapid cART therapy was found to be dominant (more effective and cost-savings) than standard path treatment regardless of the risk profile (Table 3).

Transmission risk adjusted for viral load level

Next, we carried out the analysis with the risk of MSM sexual HIV transmission adjusted for level of HIV RNA viral load (scenario A2). In this case scenario (data from Baggaley 2018 was used), the estimated avoided sexual HIV transmission rate within rapid cART therapy was from 0·013 to 0·092 compared to receiving cART immediately later. A lower transmission rate due rapid cART leads to additional QALY gained and savings costs of treatment associated with avoiding new infections. Estimated additional QALY gained due to avoid new HIV infections was from 0·022 to 0·158 depends on risk profile (low, medium and high). The additional costs savings of treatment associated with lack of new infections range from EUR896 for low risk profile to EUR 6 454 for high-risk profile.

Despite the additional costs of cART since day of HIV diagnosis related to the implementation of rapid cART, this path were associated with savings for the public payer in the amount from EUR 482 to EUR 6 041 in lifetime horizon per 1 included patients. If transmission risk was adjusted for viral load, estimated savings for national payer is even higher than in scenario when viral load was not included.

Rapid cART therapy was found to be dominant (more effective and cost-savings) than standard path treatment regardless of the risk profile (Table 3).

Patients with low level of viral load (1·70 – 3·54 log₁₀ copies/ml)

In addition, as part of the work of this analysis, calculations for group of patients with low level of viral load (50-3499 copies) were conducted (scenario A3). The estimated avoided sexual HIV transmission rate within rapid cART therapy was from 0·002 to 0·014 compared to receiving cART immediately later. A lower transmission rate due rapid cART leads to additional QALY gained and savings costs of treatment associated with avoiding new infections. Estimated additional QALY gained due to avoid new HIV infections was from 0·003 to 0·025 depends on risk profile (low, medium and high). The additional costs savings of treatment associated with lack of new infections range from EUR 141 for low risk profile to EUR 1 011 for high-risk profile.

The calculated total treatment costs of implementation of rapid cART for public payer were EUR 272 and EUR 110 for low and medium risk profiles, respectively. This means that for a group of patients with both low viral load and low risk profile, rapid cART is not a cost-effective treatment path (ICER = 78 490 EUR). In case of medium risk profile, rapid cART is cost-effective treatment path (ICER = 14 853 EUR), but not cost-saving like for high risk profile of patients (597 EUR savings for public payer per 1 included patient) (Table 3).

Sensitivity analyses

To test, whether the model is solid and the inference is sensitive we have run the calculation with three additional scenarios of the data source (Patel 2014 and Lasry 2014 for scenario S1 and scenario S2 respectively) and used Weibull distribution (scenario S3). Regardless of the analyzed scenario, the obtained results was similar to results presented in the base case scenario. When data for risk of HIV transmission from the Patel 2014 or Lasry 2014 was used and a curve of time from diagnosis to start cART was fitted to the Weibull distribution, rapid therapy was also found to be dominant (more effective and cost-savings) than standard path treatment. The estimated savings for the public payer were associated with the amount from EUR 341 to EUR 5 009 and EUR 609 to EUR 6 943 in lifetime horizon per 1 included patient for Patel 2014 and Lasry 2014 data, respectively. If additionally, the calculations were taken into account the effect of viral load (scenario S3), then the savings for the public payer ranged from EUR 452 to EUR 5820 (Table 3).

Discussion

Rapid cART is a concept of starting treatment as soon as it is possible, preferentially at the day of diagnosis, even when most of laboratory tests results are not available¹². This approach is based on three main achievements of modern cART: developing antiretroviral medicine with minimal toxicity, proving their effectiveness irrespective of CD4 count or HIV viral load and confirming that viral suppression protects HIV-negative sexual partners from acquiring.^{13–16} The most important effect of

rapid cART is improved treatment up-take and greater viral suppression, as well as improved retention in care.^{17,18} However this was well proven only for low and middle income countries, whereas adequate studies in high income countries with more complex healthcare systems are lacking.¹⁷ This is in particular relevant for Central and Eastern Europe, where most countries have more developed healthcare systems and are considered to be high income country. At the same time linkage to care in this region remains unsatisfactory and an important obstacle in adapting WHO strategy, namely providing cART to 90% of those with diagnosed HIV infection.^{19–22} WHO has already recommended rapid cART start strategy in 2017.²³ Governments and scientific societies in Europe seem to be more reluctant in adopting bold strategies due to lack of proper evidence based on local population.²⁴

Here we present that implementation of rapid cART on a national scale generates health benefits and reduces the number of HIV infections and is associated with additional savings for the payer in the lifetime horizon. In addition, falling prices of cART drugs related to expiration of patent protection for some drugs causes that the initial cost of implementation such a solution is increasingly lower. This should facilitate decision-making by the public payer.

In the case of subgroups analysis, for most of them the introduction of rapid cART is at least cost-effective or even a dominant intervention (cheaper and more effective). Only in the population of people with HIV viral load and low risk of sexual behavior, rapid cART may not be a cost-effective intervention from public payer's point of view.

There is a number of limitations which need to be considered while interpreting our data. Firstly the results obtained in a group of patients with very low viral load and a low risk of sexual behavior, rapid cART probably may not be cost-effective path. However, considering the data about characteristics of HIV patients, the percentage of such patients is very low and should not affect the results of the analysis. Moreover rapid cART seems to be especially beneficial to those at highest risk of acquiring HIV through sexual contacts, which due to changing trends in epidemic in Central and Eastern European region seems to be a key factor for HIV prevention.²⁵

It should be noted, that taking into account the impact of HIV viral load on final transmission risk was not the primary aim of this study. Hence, our assumptions and calculations in this area are characterized by some uncertainty and limitations, which is an additional area for exploration in the future. Regardless of whether rapid cART is a profitable intervention in population with the lowest risk of HIV transmission, it should be noted that people with low HIV viremia at diagnosis accounts for less than 5%-8% of those diagnosed with HIV and at least half of newly diagnosed people are presenting high risk behaviours.²⁶

The analysis included only the costs of additional cART treatment and the total costs of treating newly infected person. We did not include the other costs associated with adapting HIV treatment centers to implementation a new path of treatment or additional workload of medical staff due to the characteristics of the healthcare system in Poland. In Polish settings, other non-drug related costs in HIV treatment centers in Poland are financed on a flat-rate and it should not significantly affect the results of the analysis.

In summary, rapid cART represents a cost-effective strategy for Poland, which could be also relevant for other countries from Central and Eastern European region. In addition in the time of current COVID-19 pandemic it provides a safer option, reducing the number of necessary personal visits in the clinic and improving linkage to care.

Abbreviations

AIDS -Acquired Immune Deficiency Syndrome

AIC - Akaike information criterion

BIC - Bayesian information criterion

cART - combined antiretroviral therapy

CD4 – Claster differentiation 4

COVID-19 – Coronavirus 19 Disease

EUR - euro

HIV – Human Immunodeficiency Virus

HIV RNA – HIV ribonucleic acid

IAS-USA – International Antiviral Society – USA

IQR -interquartile range

MSM – men having sex with men

QALY- quality-adjusted life year

SARS-CoV-2 - severe acute respiratory syndrome coronavirus 2

Declarations

Ethics

This study was performed in accordance with the Declaration of Helsinki, as well as all the relevant local guidelines and regulations. The ethical approval was obtained from the Bioethical Committee of the Medical University of Warsaw (Komisja Bioetyczne Warszawskiego Uniwersytetu Medycznego) and a waiver for informed consent was granted. Information and documentation to support this statement is made available to the Editor on request. All data used in the study were fully anonymized before any of the authors had accessed them.

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Consent for publication

All authors consent for publishing this work.

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Authors' contributions:

JDK, GW, JR, ES - Conceptualization (equally),

JDK, GW, JR - Data curation

GW, JR - Formal analysis

ES - Funding acquisition

JDK, GW, JR – Investigation

JDK, GW, JR, ES - Methodology

JDK, ES - Supervision

GW, JR - Validation

JDK, GW, JR - Visualization

JDK, GW, JR - Writing – original draft

JDK - Writing - review and editing

All authors read and approved the final manuscript.

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Tables

Table 1. Baseline characteristic of newly registered patients in routine medical care 2016-2017

Parameters	Value
Mean CD4+ count [cells/mm ³] (SD)	391 (209.6)
Patients with 1.70 – 3.54 log ₁₀ HIV RNA copies/ml (50 – 3 499 HIV RNA copies/ml) [n / %]	32 (9.3%)
Patients with 3.54– 4.00 log ₁₀ HIV RNA copies/ml (3 500 - 9999 HIV RNA copies/ml) [n / %]	33 (9.6%)
Patients with 4.00 – 4.70 log ₁₀ HIV RNA copies/ml (10 000 – 49 999 HIV RNA copies/ml) [n / %]	99 (28.8 %)
Patients with >4.70 log ₁₀ HIV RNA copies/ml (50 000+ HIV RNA copies/ml) [n / %]	180 (52.3%)
Median HIV RNA [log ₁₀ copies/ml] (IQR)	4.72 (4.22 - 5.24)
Mean age [years] (SD)	33 (8.24)
Males pct. [%]	100%
MSM pct. [%]	100%

Table 2. Risk of HIV transmission when viral load is included

	Baseline risk of HIV transmission per act	1.70 – 3.54 log ₁₀ copies/ml	3.54 – 4.00 log ₁₀ copies/ml	4.00 – 4.70 log ₁₀ copies/ml	>4.70 log ₁₀ copies/ml
		[2.27 log ₁₀ copies/ml	[mean 3.76 log ₁₀ copies/ml	[mean 4.40 log ₁₀ copies/ml	[mean 5.25 log ₁₀ copies/ml
		19% basic risk]	46% basic risk]	81% basic risk]	174% basic risk]
Insertive anal sex					
Lasry 2014 ⁷	0.62%	0.12%	0.28%	0.50%	1.08%
Patel 2014 ⁸	0.11%	0.02%	0.05%	0.09%	0.19%
Baggaley 2018 ⁹	0.17%	0.01%	0.03%	0.05%	0.10%
Receptive anal sex					
Lasry 2014 ⁷	1.40%	0.26%	0.64%	1.14%	2.44%
Patel 2014 ⁸	1.38%	0.26%	0.63%	1.12%	2.40%
Baggaley 2018 ⁹	1.25%	0.26%	0.64%	1.14%	2.44%

Table 3. Results of analysis

	Incremental results / base case scenario			Incremental results / sensitive analysis		
Scenario	A1	A2	A3	S1	S2	S3
Risk profile	Medium risk (Low risk / High Risk)	Medium risk (Low risk / High Risk)	Medium risk (Low risk / High Risk)	Medium risk (Low risk / High Risk)	Medium risk (Low risk / High Risk)	Medium risk (Low risk / High Risk)
Fixed cost of rapid treatment [EUR]	0 (0 / 0)	0 (0 / 0)	0 (0 / 0)	0 (0 / 0)	0 (0 / 0)	0 (0 / 0)
Cost of cART treatment since day of diagnosis [EUR]	414 (414 / 414)	414 (414 / 414)	414 (414 / 414)	414 (414 / 414)	414 (414 / 414)	414 (414 / 414)
Cost of treatment new infections [EUR]	- 1 601 (-745 / -5 351)	-1 929 (-896 / -6 454)	-303 (-141 / -1 011)	-1 623 (-755 / -5 423)	- 2 199 (-1 022 / -7 356)	-1 863 (-866 / -6 234)
Total costs [EUR]	-1 188 (-331 / -4 937)	-1 515 (-482 / -6 041)	110 (272 / -597)	-1 209 (-341 / -5 009)	-1 786 (-609 / -6 943)	-1 450 (-452 / -5 820)
Sexual HIV transmission	-0.023 (-0.011 / -0.076)	-0.028 (-0.013 / -0.092)	-0.004 (-0.002 / -0.014)	-0.023 (-0.011 / -0.077)	-0.031 (-0.015 / -0.105)	-0.027 (-0.012 / -0.089)
LYG	0.017 (0.008 / 0.056)	0.020 (0.009 / 0.068)	0.003 (0.001 / 0.011)	0.017 (0.008 / 0.057)	0.023 (0.011 / 0.077)	0.020 (0.009 / 0.065)
QALY	0.039 (0.018 / 0.131)	0.047 (0.022 / 0.158)	0.007 (0.003 / 0.025)	0.040 (0.019 / 0.133)	0.054 (0.025 / 0.180)	0.046 (0.021 / 0.153)
ICER [EUR]	Rapid c-s (Rapid c-s / Rapid c-s)	Rapid c-s (Rapid c-s / Rapid c-s)	14 853 (78 490 / Rapid c-s)	Rapid c-s (Rapid c-s / Rapid c-s)	Rapid c-s (Rapid c-s / Rapid c-s)	Rapid c-s (Rapid c-s / Rapid c-s)

Rapid c-s = Rapid cost-savings

Scenarios description: (1. Data for HIV transmission per act / 2. Population (HIV viral load) / 3. Distribution for curve of time from diagnosis to start cART / 4. Adjusting risk transmission for HIV viral

load

Scenario A1: 1. Baggaley 2018 / 2. All patients / 3.Generalized gamma distribution / 4. No adjusted

Scenario A2: 1. Baggaley 2018 / 2. All patients / 3.Generalized gamma distribution / 4. Adjusted

Scenario A3: 1. Baggaley 2018 / 2. Patients with 1.70 – 3.54 log10 copies/ml / 3.Generalized gamma distribution / Adjusted

Scenario S1: 1. Patel 2014 / 2. All patients / 3.Weibull distribution / 4. No adjusted

Scenario S2: 1. Lasry 2014 / 2. All patients / 3.Weibull distribution / 4. No adjusted

Scenario S3: 1. Baggaley 2018 / 2. All patients / 3.Weibull distribution / 4. Adjusted

Figures

Figure 1

Simplified comparison of pathways treatment

Figure 2

Markov model for HIV treatment *They do not determine independent health states. Only additionally costs and deaths due to cardiovascular events and other illnesses were charged, regardless of the state of health in each cycle of analysis.

Figure 3

Time from diagnosis to start cART treatment