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STRUCTURED TREATMENT INTERRUPTIONS: AFTER SMART

The recent termination of several major studies of structured treatment interruption (STI)—the term for taking a planned break from anti-HIV medications—has drawn heightened attention to this treatment strategy. Always a controversial and intriguing approach, STI has been the focus of large-scale trials only in the last several years. Since January, three such studies have been halted early after researchers found that individuals who stop and start highly active antiretroviral therapy (HAART) are at greater risk for HIV disease progression and serious illness than those who take treatment continuously. However, other studies show that many questions remain about the risks involved. There is still considerable interest in both the research and HIV positive communities in better understanding the effects of interrupting anti-HIV therapy. This article provides an overview of STI, including some of the recent research findings, and examines several issues that people contemplating a break from treatment should consider.

Renewed Debate

At the 13th Annual Conference on Retroviruses and Opportunistic Infections, held in Denver this past February, John Bartlett, MD, Chief of the Division of Infectious Diseases at Johns Hopkins University and a pioneer in HIV medicine, declared in his plenary remarks that all studies to date on interrupting HIV therapy had soundly failed. His comment felt particularly definitive as it came only weeks after enrollment in the largest STI study ever conducted—the Strategies for Management of Antiretroviral Therapy trial, or SMART—had been discontinued. A review by the study's Data and Safety Monitoring Board (DSMB) found that participants who took intermittent

treatment were at significantly increased risk for HIV disease progression and death than those who remained on continuous treatment.

Yet the highly publicized cancellation of the SMART trial has hardly put an end to the STI debate; individuals on both sides can find evidence in that study and others to bolster their positions. Some declare that STI is too dangerous to consider, while others claim it will inevitably occur at some point in a lifelong course of medication. In spite of the SMART trial findings, data from several other STI studies also reported at the Retrovirus conference showed that the effectiveness of treatment interruption, as well as its safety, cannot be so easily dismissed.

Early STI Studies

Ever since combination antiretroviral therapy was shown to be effective and became widely available, people have been trying to get off their drugs. There are many reasons. Some are physiological: side effects and drug toxicity can make it impossible, and sometimes even deleterious to health, to remain fully adherent. Other reasons are psychological: the complex, burdensome, and endless regimens of anti-HIV medications can lead to treatment exhaustion and the desire to take a break. Simple cost savings, especially in resource-limited communities and countries, are another compelling reason some investigators are interested in examining treatment interruption.

How the Body Reacts to a Treatment Interruption

Diminishment of HAART-related side effects.

One immediate effect of treatment breaks is that some side effects, such as fatigue and diarrhea, are reduced.

Viral load rebound.

As soon as anti-HIV medications leave the body, the virus begins to replicate. Viral load can shoot up sharply, often to pre-treatment levels.

Acute retroviral syndrome.

As viral load rises, it can trigger an immune response and flu-like symptoms, such as fever, swollen lymph nodes, and weakness. Some people experience this acute retroviral syndrome when they go off anti-HIV medications, just as many do when first infected with HIV.

CD4 cell decrease.

Typically, the number of CD4 cells begins to fall rapidly in the first weeks after starting a treatment break, followed by a much more gradual loss over the long term. The CD4 count at the beginning of a treatment break often determines the duration of the interruption period.

HIV-associated conditions.

Falling CD4 cell count makes people taking treatment breaks more susceptible to opportunistic illnesses, such as herpes zoster (shingles), herpes simplex, and candidiasis (thrush), as well as other conditions, including thrombocytopenia (low blood platelet count).

However, the first studies of STI did not focus on practical benefits or quality of life; rather, they investigated whether treatment breaks actually improve the body's ability to fight the virus (see "Structured Treatment Interruptions: Protocol or Wishful Thinking," in the Spring 2000 issue of *BETA*). One theory—called "auto-immunization"—held that intermittent treatment could in fact boost the immune system's response to HIV by

exposing it to a series of viral rebounds. Since effective HAART successfully suppressed the virus to extremely low levels, the hypothesis went, the immune system never had the chance to mount a response. These early studies took participants off of their medications for fixed periods to allow viral load to increase and then be resuppressed, measuring immune response over time. Despite some small studies indicating that

this strategy might prove effective, this avenue of research was all but abandoned after the large Swiss-Spanish Intermittent Treatment Trial yielded negative results.

A second area of interest in STI concerned its possible uses for treatment-experienced individuals who had developed multidrug-resistant HIV. Various studies showed that when treatment was interrupted in people who had developed resistance, their virus often reverted to wild type (i.e., without resistance mutations) in the absence of medication. In a number of these individuals, the wild-type virus could then be suppressed once again with reinitiation of HAART. In the GigHAART study, Christine Katlama, MD, of the Pitié-Salpêtrière Hospital in Paris and colleagues successfully employed this strategy prior to initiating an aggressive salvage therapy regimen. However, during the treatment interruption period, study participants were highly susceptible to opportunistic infections (OIs). Further investigation has shown that resistance mutations are quick to reestablish themselves once HAART has been restarted.

Because the early STI studies were small, they offered provocative but hardly conclusive evidence. By the time the larger studies such as SMART got underway, the theories of autoimmunization and STI as a pre-salvage strategy were already fading. Nevertheless, investigators hoped to learn more about the safety of treatment interruptions and how they might be used to spare HIV positive people the costs—of all types—of being on continuous HAART. For that reason, the first reports from these larger trials have been awaited with great anticipation.

Seven Recent Reports

Because the SMART trial was the largest and most ambitious STI study to date, its findings carry particular weight and cannot be ignored. Data from a number of other ongoing STI

studies were also presented at the Retrovirus conference, and these results were as varied as the study designs.

The SMART Trial

By January 2006, nearly 5500 HIV positive individuals out of a planned total of 6000 had been recruited for the multinational SMART trial, sponsored by the National Institutes of Health. Participants enrolled at 318 sites in 33 countries. The purpose of the trial was to examine the effects of CD4-guided intermittent treatment compared with continuous therapy, thereby identifying the best strategy for maintaining CD4 cell counts above a specified threshold while minimizing the risks of using HAART. All participants began the study with CD4 cell counts higher than 350 cells/mm³, and nearly all (95%) had previously been on anti-HIV medications. The study included a wide range of HIV positive individuals, including those who had a prior AIDS diagnosis, those with drug-resistant virus, and those with a CD4 nadir (lowest-ever level) below 150 cells/mm³.

Participants were randomly assigned either to maintain a continuous HAART regimen or to stop and start treatment based on their CD4 cell counts. In the treatment interruption arm, participants stopped taking HAART at enrollment until their CD4 counts fell to 250 cells/mm³, at which time they resumed treatment. When their CD4 counts rose to 350 cells/mm³, they again stopped treatment. These participants had a median of three treatment interruptions, with a median length of 18 months per interruption. The hope was that people who received treatment intermittently would maintain good health with fewer side effects and less drug toxicity.

The DSMB halted enrollment in the study in January after a median of 14 months of follow-up, and recommended that all participants in the STI arm shift to continuous treatment. The

incidence of serious medical events, HIV disease progression, and death were found to be more than twice as high in those undergoing intermittent HIV treatment, with 117 cases (3.7%) compared with 47 cases (1.5%) in the continuous treatment arm. Because the study was large, this difference was highly statistically significant. The DSMB concluded that the risk to participants was serious enough to recommend stopping the study.

Overall, participants in the STI arm spent 33% of the time on treatment, compared with 93% in the continuous treatment arm; however, they spent over three times longer at CD4 levels below 350 cells/mm³. It is not entirely surprising that this group experienced a higher incidence of AIDS-related conditions, such as candidiasis. But one truly unexpected result was the increased number of non-AIDS-related medical complications—such as cardiovascular, liver, and kidney problems—in the interruption arm: 59 episodes (2.1%) in the STI arm compared with 37 (1.4%) in the continuous treatment arm. These kinds of complications are typically associated with HAART, and it was expected that participants in the continuous treatment arm would experience them more frequently.

Principal Investigator Wafaa El-Sadr, MD, MPH, Chief of the Infectious Diseases Division at Harlem Hospital, suggested that increased levels of inflammation, caused by higher viral loads in the treatment interruption group, might be responsible for the increased incidence of severe complications, such as cardiovascular disease. However, this is very preliminary speculation; the cause is unknown and still mysterious.

The overall risk of disease progression did not differ based on gender, race, CD4 cell count at enrollment, or prior AIDS diagnosis. Another surprise was that it was also unaffected by nadir CD4 cell count. This was unexpected, since previous STI studies have shown that patients with low

nadir CD4 cell counts are at greater risk for disease progression.

One factor that was linked to an increased risk of disease progression was HIV viral load at enrollment. At the start of the study, 70% of participants had viral loads less than 400 copies/mL. Among these individuals, the CD4-guided treatment interruption arm had a risk of disease progression nearly four times greater than that of the continuous therapy group. In contrast, among participants entering the trial with viral loads above 400 copies/mL, there was no difference in disease progression between the two study arms.

Although recruitment into the SMART study has stopped and those in the treatment interruption group are being urged to switch to continuous therapy, the investigators will continue to follow study participants and monitor the effects of treatment interruption over the long term. A substudy of SMART will also analyze quality of life as perceived by participants in the trial; these results may help elucidate the larger life context and benefits for those attempting treatment interruption.

Trivacan Trial: STI in a Resource- Limited Setting

The Trivacan trial is one of two STI studies currently taking place in sub-Saharan Africa. Initially, the plan was to compare two STI strategies—CD4-guided and fixed-length cycles—with continuous HAART. As with the SMART trial, the CD4-guided treatment interruption arm of the study was halted early after an increased risk of serious illness and death was observed.

The study, sponsored by the French National Agency for AIDS Research (ANRS), recruited 840 participants in the Ivory Coast capital of Abidjan. In this trial, 70% were women and 35% had advanced HIV disease. All participants were treatment-naïve at enrollment, with CD4 cell counts between 150 and 350

cells/mm³. Participants were initially started on HAART for at least six months, until CD4 count rose above 350 cells/mm³ and viral load fell to less than 300 copies/mL. Individuals were then randomly assigned to one of the three arms: 1) continuous treatment with antiretrovirals; 2) CD4-guided intermittent treatment, stopped at 350 cells/mm³ and resumed at 250 cells/mm³; and 3) fixed cycles of treatment interruption, with two months on followed by four months off.

Participants were followed for 96 weeks. After 19 months of follow-up, those in the CD4-guided interruption arm were found to be more than twice as likely to experience serious illness—including invasive bacterial infections, candidiasis, and tuberculosis—as those on continuous HAART. This STI arm also had twice the death rate. The Trivacan study's DSMB recommended halting the CD4-guided treatment interruption arm; the fixed-length treatment interruption and the continuous treatment arms are ongoing.

Staccato Trial Shows More Promise

Though less ambitious in size, the Switzerland Thailand Australia Collaborating Countries Alternative Treatment Options (Staccato) trial presented more promising results for a CD4-guided treatment interruption strategy than either SMART or the Trivacan study. This study recruited 430 participants with CD4 counts greater than 350 cells/mm³ and viral loads less than 50 copies/mL. Subjects were randomly assigned to either continuous therapy or episodic treatment based on CD4 count. (Initially, the study also included a fixed-length week-on, week-off interruption arm, but this was quickly discontinued because an increased risk of drug resistance was seen.)

Median CD4 counts at enrollment were 470 cells/mm³ for the STI arm and 507 cells/mm³ for those on continuous HAART—much higher than in the Trivacan study. Another important

distinction between Staccato and the SMART and Trivacan trials concerns the CD4 cell level at which those undergoing treatment interruption resumed therapy. In both SMART and Trivacan, participants restarted HAART when their CD4 count fell to 250 cells/mm³; however, in the Staccato trial, participants restarted at 350 cells/mm³. The results were strikingly different. In this study, patients in the episodic therapy arm managed to take drugs for 62% less total time than those in the continuous therapy arm, while avoiding the serious illnesses encountered in the other trials. Though AIDS-related illnesses, including vaginal and oral candidiasis and thrombocytopenia, were more frequent in the treatment interruption arm, no AIDS-defining illnesses were observed in either group. Nor was there evidence of emerging drug-resistance mutations in the STI arm.

Aside from the criteria for starting and stopping anti-HIV treatment in the STI groups, there are a number of other differences between SMART and Staccato that might explain their discordant results, including the makeup of the study populations, prior treatment experience, extent of disease progression before the study, and drug regimens used by participants.

ACTG 5170: An Extended Break

The AIDS Clinical Trials Group (ACTG) study 5170 looked at a single treatment interruption of 96 weeks for individuals with CD4 counts greater than 350 cells/mm³ and viral loads less than 55,000 copies/mL. All 167 participants in this study had been on continuous HAART for at least six months and desired to stop. At enrollment, the median CD4 count was 833 cells/mm³ and the median CD4 nadir was 436 cells/mm³.

After stopping treatment, participants' CD4 cell counts declined following a pattern seen consistently in other studies: an initial rapid decline (of 198 cells/mm³ on average) during the first eight weeks, followed by a

much more gradual decline (a mean of 1.74 cells/mm³ per week) over the ensuing months. Treatment interruption was found to be relatively safe in this group, with a few AIDS-related and non-AIDS-related events occurring after treatment was stopped (including thrombocytopenia, herpes zoster, bacterial infection, and hypertension). Five of the study participants died, but none of the deaths were directly attributed to HIV/AIDS. However, at least three of these five deaths involved cardiovascular disease; in light of the SMART trial findings, it is not entirely certain that these deaths were unrelated to stopping treatment. In contrast to the SMART study, in ACTG 5170 having a CD4 nadir below 400 cells/mm³ was highly predictive of faster CD4 decline or clinical events following the interruption of treatment.

Window Trial Looks Safe

The Window trial, also conducted by the French ANRS, took a different approach to STI by using fixed-length cycles of intermittent therapy compared with continuous HAART over 96 weeks.

The study recruited 403 participants, 80% of whom were men, who had CD4 counts greater than 450 cells/mm³ and HIV viral loads below 200 copies/mL for six months prior to enrollment. The median CD4 count was 745 cells/mm³ and the median CD4 nadir was 280 cells/mm³. Study participants were randomly assigned to two groups: one receiving continuous therapy for 96 weeks, the second receiving intermittent therapy for eight weeks, followed by eight weeks of treatment interruption.

Participants in the STI arm experienced a median CD4 decline of 155 cells/mm³; 3.5% of them fell to CD4 counts below 300 cells/mm³, compared with 1.5% in the continuous treatment arm. Yet there were no AIDS-defining illnesses in either group, and both groups experienced roughly equivalent—and curiously

high—rates of emergent drug resistance (17% of STI participants, 14% of those on continuous HAART). Here again, more instances of AIDS-related conditions—thrombocytopenia, acute retroviral syndrome, and candidiasis—were seen in the STI group, as was the case in other studies. Overall, however, a treatment interruption of 96 weeks was shown to be clinically safe in this trial, while reducing drug exposure by nearly 50%.

Resistance Seen in Italy

The Istituto Superiore di Sanita (ISS) PART study, conducted at various clinical sites in Italy, compared continuous therapy with a series of treatment interruptions of increasing duration—one, two, and three months. Each interruption was followed by three months of antiretroviral therapy. The study recruited 273 individuals who had been on HAART for an average of two years, with CD4 counts greater than 700 cells/mm³, CD4 nadirs greater than 400 cells/mm³, and viral loads less than 400 copies/mL. The participants were randomly assigned to the two study arms. After 24 months, 86% of those on continuous therapy had CD4 counts greater than 500 cells/mm³, compared with 69% in the STI arm.

Unsurprisingly, a higher CD4 cell count at the beginning of the study was predictive of slower disease progression during treatment interruptions. However, unlike most of the other trials presented at the conference, the ISS-PART study found a very high rate of drug-resistance mutations in the STI arm. Of the 136 individuals undergoing STI, 33 (30%) developed such mutations, and they were more than twice as likely as participants who did not develop resistance to experience virologic failure when they resumed therapy. Use of an unboosted protease inhibitor (PI) was strongly associated with the emergence of resistance.

DART Misses the Target

The Development of Anti-Retroviral Therapy in Africa (DART) study is an ongoing five-year clinical trial conducted through a collaboration of African and British hospitals, with 3300 participants in Uganda and Zimbabwe. Its primary objective is to evaluate different methods of monitoring the use of antiretroviral therapy, but it also includes an STI substudy comparing continuous treatment with cycled treatment interruptions of 12 weeks off HAART and 12 weeks on.

In March, shortly after the Retrovirus conference, the treatment interruption arm of DART was terminated (although the main aspect of the study on monitoring HIV disease progression will continue), and all participants were advised to switch to continuous treatment. This occurred for much the same reason as the early termination of SMART; the study's DSMB found in its review that participants taking treatment breaks were much more likely to experience HIV-related illnesses than those on continuous treatment.

A total of 799 HIV positive individuals were recruited into the treatment interruption substudy. At enrollment, participants were treatment-naïve and had CD4 counts less than 200 cells/mm³. All began antiretroviral therapy, and after 12 to 18 weeks achieved CD4 cell counts above 300 cells/mm³. At that time, they were randomly assigned either to stay on continuous antiretroviral therapy or to begin cycled STI.

Participants in the STI arm experienced four times as many instances of HIV-related disease—candidiasis being the most common—compared with those in the continuous therapy arm (25 vs 6 subjects). There was one death in each of the two arms. Further analysis of this study will be presented at the International AIDS Conference this August in Toronto.

Comparing Apples and Oranges

Given such a mixed bag of studies, methodologies, and results, it is difficult to come to useful conclusions about the effectiveness and risks of STI. To pronounce all STI studies failures, however, appears not only simplistic, but even slightly moralistic in tone. While it is obvious that caution should be exercised when stopping treatment for whatever reason, a number of themes emerged from these studies that can help guide both clinicians and patients when thinking about the subject of treatment interruption.

CD4-Guided STI vs Fixed-Length Cycles

Two of the cancelled STI trials—SMART and one component of the Trivacan study—looked at CD4-guided treatment interruption, which has led some to conclude that this STI strategy is especially dangerous. Only one of the fixed-length interruption studies—the DART substudy—was cancelled because of increased health risk, while the other cycled-interruption studies did not show increased risk for adverse events or disease progression.

The primary difference between the cancelled STI trials and the CD4-guided Staccato trial, as mentioned above, is that participants in the cancelled trials did not resume HAART until their CD4 levels fell to 250 cells/mm³, while the Staccato trial participants restarted antiretroviral treatment at 350 cells/mm³. It is possible that individuals living for longer periods with lower CD4 counts are more susceptible to infections and illnesses. However, in her remarks about the SMART study, El-Sadr emphasized that it is still premature to conclude that STI is safer at the higher threshold.

Another notable factor is that participants in CD4-guided STI studies are typically off treatment for much

longer periods than those in fixed-length studies. For example, in the ACTG 5170 trial, participants went off HAART for a median of 96 weeks, while in the fixed-length trials the treatment breaks ranged from one to three months. In fact, the trial of this type that had the longest treatment hiatus—the DART trial, which cycled in periods of three months on and three months off—also showed the greatest number of adverse events.

CD4 Nadir

Previous studies have shown an association between the lowest CD4 cell count an individual has ever experienced and success during STI. Lower CD4 nadirs predicted faster CD4 count decline and a quicker resumption of HAART. Several of the smaller studies produced results that did not diverge from conventional thinking. The ACTG 5071 and PART studies, for example, both found that CD4 nadir was predictive of AIDS-related conditions and AIDS-defining illness.

Therefore, it was very surprising to find in the SMART trial that CD4 nadir did not predict HIV disease progression. Because the study was so large, these results certainly open the door for new hypotheses about the long-term effects of low CD4 count, even if they do not completely overturn current beliefs.

Costs and Benefits

If there is anything consistent or clear about all the STI studies presented, it's that they greatly cut down on drug exposure and cost—by half or even more. Several approaches seemed to limit drug exposure without entailing detrimental effects on health, though as of yet there have been no quality-of-life studies that can define other benefits for individuals taking a break from treatment. Drug side effects, such as diarrhea, were generally seen less often in the STI arms than in the continuous treatment arms, while more instances of non-hospitalizable AIDS-related illnesses, such as candidiasis, were seen

in those interrupting treatment. No real surprises there.

The shocker came in the SMART trial findings. To see elevated rates of clinical events such as cardiovascular, kidney, and liver problems in the STI group—when it has generally been agreed that these are side effects associated with HAART—turns common wisdom on its head. No one really knows yet what this means, and a number of investigators may now take a new look at their data. For example, the deaths attributed to non-AIDS-

related cardiovascular disease in the ACTG 5170 trial could turn out to be something more disturbing. Unfortunately, because this finding is so recent, it will be some time before more is known.

Resistance and Other Drug Considerations

An obvious concern with any treatment interruption is the risk of developing drug resistance. However, most of the studies presented at the Retrovirus conference showed very low

Risks of Treatment Interruptions

- Decrease in CD4 cell count, often rapid
- Increase in HIV viral load
- Higher viral load could lead to opportunistic illnesses
- Increase in HIV viral load can cause acute retroviral syndrome, or flu-like symptoms
- Higher risk of developing drug resistance
- Higher risk of experiencing virological failure when resuming HAART
- Possible higher risk of cardiac, liver, and kidney problems (still unclear)

Benefits of Treatment Interruptions

- Reduced drug side effects or toxicity
- Relief of treatment fatigue or reduced adherence
- Accommodation of unusual schedule because of travel or other reasons
- Reduced monetary cost of drugs and medical care
- Use as part of a salvage regimen strategy

rates of emergent resistance mutations, though the PART study did have an alarmingly high incidence in its STI arm.

At enrollment in the PART study, participants had been on antiretroviral therapy for an average of two years; 70% were using a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen, and the rest were on unboosted PI-based HAART. Due to the long half-life of NNRTIs, efavirenz (Sustiva) was stopped six days earlier than the other drugs, and nevirapine (Viramune) was stopped three days earlier. It is unclear why 30% of participants developed resistance mutations, though the emergence of mutations was associated with the use of an unboosted PI; 50% of participants on unboosted PIs developed mutations, compared with 20% of those on NNRTIs.

In contrast, few resistance mutations were recorded in the Staccato trial, in which 80% of the participants were on a boosted-PI regimen: ritonavir (Norvir)-boosted saquinavir (Invirase) along with two nucleoside reverse transcriptase inhibitors (NRTIs). Boosted PI-based HIV treatment shows a high barrier for resistance.

An important consideration for anyone interested in a treatment break is the half-life of HIV medications. It takes a variable amount of time to metabolize and clear different antiretrovirals from the body. If all medications in a combination regimen are stopped abruptly, the levels of some may diminish more quickly than others, opening the door for the development of resistance to those drugs that linger longer at low amounts. The NNRTIs efavirenz and nevirapine and the NRTI tenofovir (Viread) can take up to a week after treatment is stopped for levels to decline below the minimum inhibitory concentration. Therefore, when contemplating a treatment interruption, people should work with their doctors to create an appropriate schedule for discontinuing the specific drugs in their HAART regimen.

Conclusion

So, what now? After the presentations at the Retrovirus conference, a panel of STI experts discussed possible directions for the next wave of investigations. Several researchers thought it apparent that the lower CD4 cell thresholds for restarting CD4-guided therapy in the SMART and Trivacan trials put people at too much risk for disease progression. But that does not necessarily require abandoning the idea of CD4-guided interruption altogether. What is needed now is SMART II, using a higher CD4 cell threshold for resuming HAART. However, as El-Sadr, one of the principal investigators of SMART, emphasized, we cannot automatically assume that this is a safer strategy.

The most worrisome issue raised by SMART—the increase in cardiovascular, liver, and kidney problems in those taking a treatment break—has opened up a new area of investigation. The cause could turn out to be, as El-Sadr suggested, an increased inflammatory response due to higher HIV viral load, but it is still too early to know. Whatever the reason for these clinical events, it underlines once again that beliefs about HIV disease—in this case, that these medical problems are only associated with HAART use—are always open to question.

Few of the researchers investigating STI argue that treatment interruption is preferable to continuous HAART for controlling progression of HIV disease. Rather, over the last decade, thinking on STI has shifted more toward a harm reduction strategy. Even with the risks involved, people will continue to take treatment breaks, and the need to understand the best ways to conduct them will continue to drive further studies. As the DART investigation team stated in the press release announcing the closure of its STI substudy, “the need to interrupt therapy for multiple reasons, e.g., drug toxicity, is likely to remain an integral part of life-long treatment of HIV disease. Finding out how and

when therapy can be interrupted safely and which patients may benefit from such strategies are still important questions and should be pursued in future trials.”

Michael Sledge is the guest editor of the Winter 2006 issue of BETA.

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