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Eradication and Cure of HIV

STEPHEN J. KENT

KEY CONCEPTS

p0010 • Lifelong antiretroviral therapy is expensive and has side effects; an ability to cure HIV is highly desirable.

u0015 • HIV can stably integrate and remain latent in resting CD4 T cells – this is a major barrier to cure.

u0020 • Bone marrow transplantation has been able to provide a sterilizing cure of HIV in one subject.

u0025 • Very early treatment shows promise in HIV-infected babies as a pathway to at least a transient functional cure ('remission') of HIV.

u0030 • Several antilatency drugs are being developed primarily to activate latent HIV and lead to reductions in numbers of latently infected cells.

u0035 • Gene therapy approaches to curing HIV are also under development.

u0040 • HIV may never readily be cured but there is an intense research effort ongoing to understand if curing HIV is feasible.

s0010 1 Introduction

p0050 Great strides have been made in the suppression of HIV infection using combination antiretroviral therapy (cART) in the last 20 years. However, the current cART paradigm has several problems. These include the need for lifelong therapy and attendant compliance problems, expense, side effects, development of drug resistance, the lack of normalization of chronic inflammatory markers, low level residual viral replication, higher rates of cardiovascular, hepatic and renal conditions, and higher rates of cancer. These issues combine to result in a suboptimal life expectancy in HIV-infected subjects. The ability to safely and inexpensively cure HIV would be a quantum advance and greatly assist in the control of the HIV epidemic.

p0055 It must be stated from the outset that HIV may never be able to be safely or inexpensively cured for reasonable numbers of subjects. Sometimes hype can exceed reality in medical research. There are, however, reasons to be hopeful, in part because a markedly increased level of research and resources is being applied to this issue in recent years.[1]

p0060 There are many barriers to the cure of HIV. HIV can stably integrate into resting CD4 T cells where it is hidden from current cART agents, which can only act on replicating virus.[2,3] Resting memory CD4 T cells have a very long lifespan since they form part of our lifelong immunological memory. The latent HIV reservoir under cART appears to have a very long half-life (decades) and does not appreciably decay.[4] Latent HIV exists in multiple tissues and organs (including the brain and the gut), although latent HIV has been most studied in blood-resting CD4 T cells. Low level HIV replication despite cART and chronic inflammation may assist in maintaining levels of the latent HIV reservoir.

p0065 There are two broad approaches to curing HIV – sterilizing and functional. A sterilizing cure is the classical infectious disease model of cure where all virus elements would be gone. A functional cure is where there may be residual virus but the virus is maintained in a quiescent state without the need for cART. A functional cure is akin to subjects with nonprogressive HIV, typically where immune responses maintain virus replication at low or undetectable levels.

p0070 There are several approaches currently in clinical trials studying aspects of cure of HIV. These can be broadly categorized as bone marrow transplant approaches, early cART therapy approaches, antilatency drug therapy approaches, immune manipulation approaches and gene therapy approaches. They are summarized in Table 105-1.

s0015 Bone Marrow Transplantation to Cure HIV

p0075 The most celebrated case of apparent HIV cure is the 'Berlin patient'.[5] This HIV+ man developed a leukemia requiring a bone marrow transplant (BMT) and his physicians chose a donor lacking expression of CCR5, a key HIV entry receptor. His cART was stopped after the BMT and HIV viremia had not recrudesced after several years. Minimal or no HIV has been detected in both blood and other organs for many years off cART[6] (Figure 105-1). This anecdotal case of essentially sterilizing cure of HIV suggests that primary HIV reservoir may xist in immune cells that were lost either as a result of the chemotherapy/radiotherapy induction for the BMT and/or as a result of subsequent graft versus host disease.

p0080 Two further cases of BMT for malignancy in the setting of HIV infection have been reported from a Boston group.[7] In these two cases the donor was not devoid of CCR5. Both subjects had low or undetectable levels of HIV after the transplantation while on cART and were subsequently taken off cART. However, after a period of a few months off cART it has recently been reported that HIV viremia was re-established. It is not yet clear if a lack of CCR5 in the donor or some other features of the BMT conditioning regimen or graft versus host disease will be needed to replicate the success of the Berlin patient. Although BMT is not a viable method to cure HIV, having both very high costs and very high morbidity and mortality, lessons learned from HIV+ subjects undergoing BMT may ultimately find application in safer and less expensive therapies.

s0020 Early Treatment of HIV to Control HIV off cART

p0085 The next most celebrated case of apparent HIV cure is the 'Mississippi baby'. This infant was born to a mother who found out she was HIV+ during labor (Figure 105-2). The infant had high levels of viremia at birth and was treated within hours with a triple combination of cART.[8] The infant subsequently stopped cART some 18 months later when medical care was lost. Upon subsequent testing at 24 months of age and beyond, viremia remained undetectable with minimal to no levels of residual HIV DNA detectable off cART. HIV antibodies declined and no infectious HIV could be recovered from culturing large numbers of cells. However, recent data shows that HIV rebounded 27 months later and cART was re-initiated.[9] The case suggests that, at least in some cases, very early initiation of cART may substantially reduce the latent reservoir of integrated viral DNA. Although speculative, this may allow remaining immune responses or other host mechanisms to clear residual latent reservoirs. Wider studies are now planned on HIV-infected babies to evaluate whether this scenario can be replicated and the conditions needed.

p0090 Early treatment of adults with HIV infection has also been postulated to assist in the functional cure of HIV off cART.[10] A small number of subjects were studied by Walker and colleagues in the year 2000 with

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TABLE 105-1

Antilatency Strategy	Concept	Advantages	Disadvantages	Current Status	References
Bone marrow transplantation	Replacing bone marrow with HIV– bone marrow which lacks CCR5 both eliminates much of the reservoir and provides no new targets for new infection	One well-documented case of HIV cure (Berlin patient)	High morbidity and mortality from procedure – only done in subjects with malignancy. CCR5 negative donor may be required	Being studied on case-by-case basis	5
Early treatment of HIV	Very early treatment with cART after infection may limit size of the latent HIV reservoir such that virus recrudescence does not occur off cART	One well-documented baby transient functional cure after cART initiated early after birth	Defining subjects with very early HIV infection difficult. Treatment of adults after a few weeks of infection has modest benefit	Expanded studies of babies born to HIV+ mothers planned	8
Antilatency drug approaches	Administration of drugs to reactivate and clear latently infected cells	Trials show an increase in HIV expression after use of drug vorinostat Multiple drugs under development	Impact of single drugs on total reservoir may be low. Safety concerns with some drugs	Multiple clinical trials underway	15
Immune manipulation	Enhancing HIV immunity to clear reactivated latently infected cells	Promising macaque-SIV studies with T cell-based vaccines and antibody infusions	No proof of concept in clinical trials	Translation to clinical trials underway	20,22
Gene therapy approaches	Eliminating CCR5 expression to render cells noninfectable	First clinical trial shows some promise in reducing viremia off cART	Small studies to date. Somewhat complex cell manipulations may be required	Expanded trials underway	24

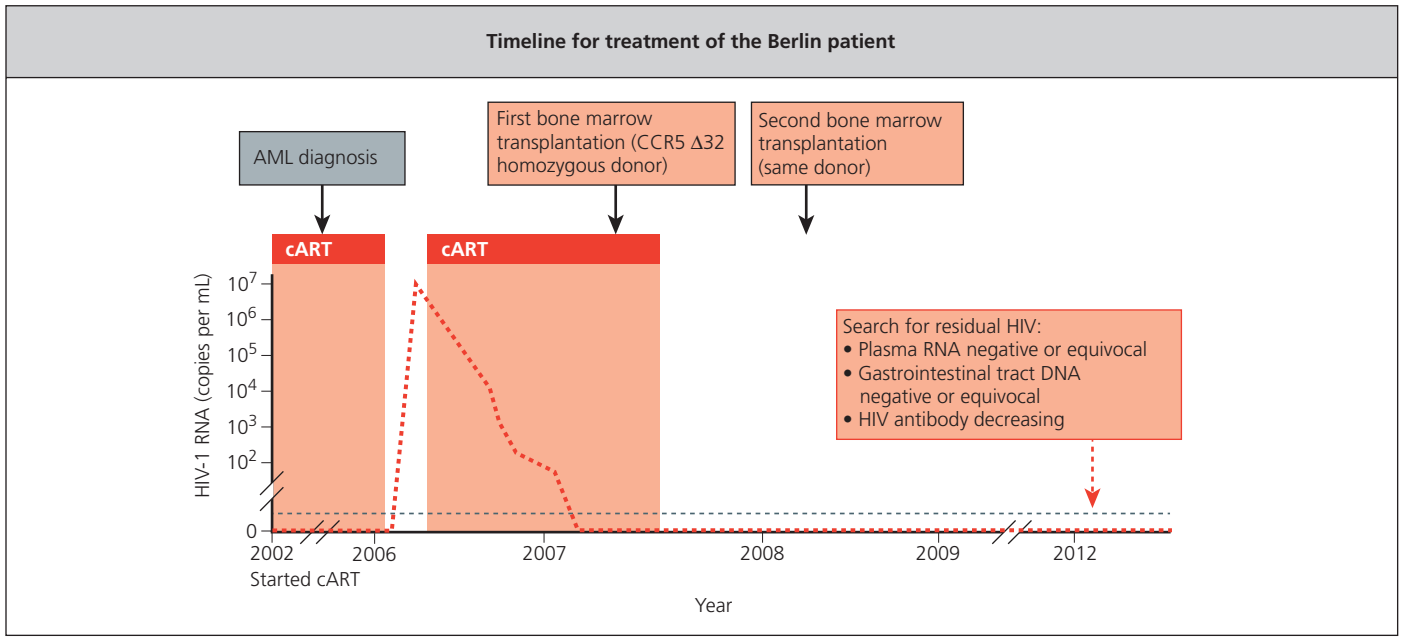

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Figure 105-1 Timeline for treatment of the Berlin patient. The grey dotted line represents the limit of detection (one copy per mL) in tests used after transplantation. AML=acute myeloid leukemia; cART=combined antiretroviral therapy. *(From Kent S.J., et al.: The search for an HIV cure: tackling latent infection.* Lancet Infect Dis *2013 Jul; 13(7):614-21.)*

the suggestion that early treatment facilitated improved generation of anti-HIV immunity.[11] HIV-specific CD4 T cell responses were preserved by cART since these cells are good targets for HIV infection and are often depleted. Eventual cessation of cART in this early group of subjects did not result in viral rebound. However, subsequent larger controlled trials by this group failed to confirm that early treatment resulted in significant numbers of subjects with durable control of viremia.[12] A recent large randomized trial does suggest that subsequent set point viremia levels can be lowered by early treatment, but the effect is not dramatic and uncommonly leads to a functional cure.[13] A French group has also reported on a selected set of subjects who were treated early and control HIV off cART.[14] This group (the 'Visconti' cohort) appears to have low but detectable levels of HIV DNA. The conditions needed to replicate these findings in a controlled setting are not yet clear.

Antilatency Drug Approaches

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There are several trials reported and ongoing with agents designed to activate and kill latently infected cells in subjects on cART. Drugs with the ability to inhibit histone deacetylase (HDAC) have been studied in particular. The antiepileptic drug valproate was initially studied with

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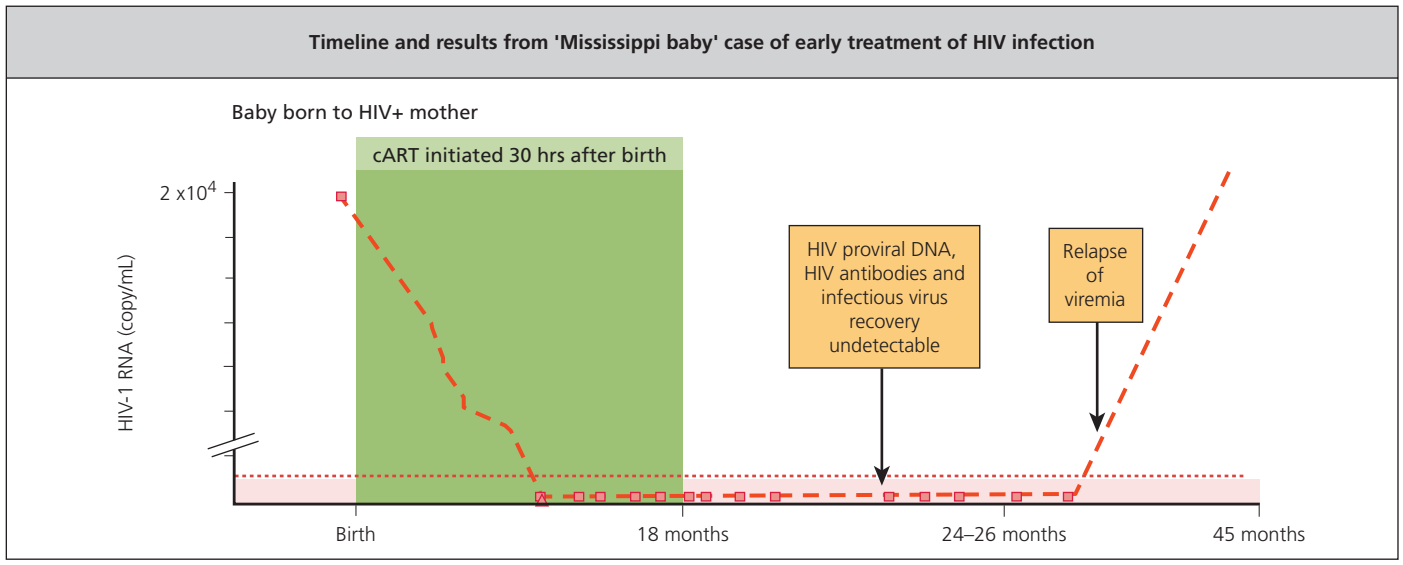

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Figure 105-2 Timeline and results from the 'Mississippi baby' case of apparent HIV cure.

some promise in small studies but later found to have no effect on the reservoir size.[15] Two other HDAC inhibitors, vorinostat and panobinostat (both anticancer drugs) have been studied in three trials and have shown evidence of low levels of HIV reactivation but are likely to have only modest effects on the total latent reservoir size.[16] No subjects from these studies have been taken off cART to assess whether viral rebound occurs. An additional HDAC inhibitor, romidepsin, is in clinical development.

p0100 There are several other potential targets by which to activate latent HIV that are also under development. The anti-alcoholism drug disulfiram activates protein kinase AKT to reactivate latent HIV and is in clinical trials in HIV-infected subjects on cART.[17] There is significant interest in developing additional antilatency drugs and additional targets under development include methylation inhibition, histone methyltransferase inhibitors, activators of NF-κB and cytokines such as IL-7. Combinations of such approaches (as is done with cART) may ultimately be needed to activate sufficient latent HIV to substantially affect the latent reservoir such that HIV viremia does not recrudesce after cART cessation.

p0105 The timing of administration of antilatency drugs has also been recently highlighted. Macaque-SIV studies have suggested that in the absence of cART the population of SIV DNA in resting CD4 T cells may be quite labile and more amenable to clearance.[18] This contrasts with the very stable and fixed population of latently infected cells on cART. This has led to the proposal of administering antilatency drugs at the initiation of cART, rather than after long-term cART, as is currently the case.[19] Combining such an approach together with studying patients during early infection (where levels of latent virus may be lower and more amenable to change) and the use of vaccine or immune therapies may result in a more substantial impact on the latent HIV reservoir.

s0030 Immune Manipulation to Reduce the Latent Reservoir

p0110 An intriguing question about some antilatency drug approaches is whether the latently infected cells actually die after reactivation or return to a latent state. It is possible that immune mechanisms will be needed to help clear the latently infected cells that are reactivated (Figure 105-3). Shan *et al.* showed *in vitro* that activated cytotoxic T cells (CTL) could recognize and kill latently infected cells reactivated with HDAC inhibitors.[20] This suggests that vaccines or other immune manipulations could act in concert with antilatency drugs to improve their efficacy. Picker and colleagues have recently shown that

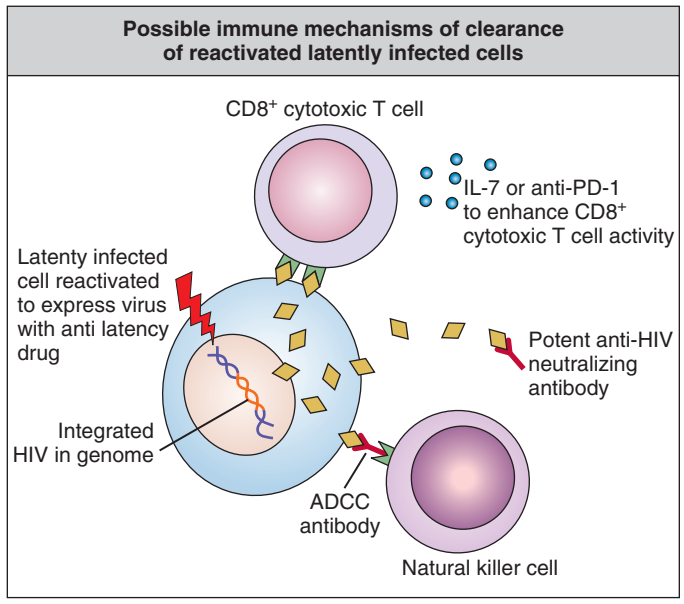

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Figure 105-3 Possible immune mechanisms of clearance of reactivated latently infected cells.

CMV-based SIV vaccines can induce high levels of activated CTLs and lead to a gradual but complete clearance of both replicating and latent forms of SIV in a subset of vaccinated monkeys.[21] Improving the efficacy of T cell approaches could be achieved using cytokines such as IL-7 or blockers of the programmed cell death receptor PD-1.[22]

p0115 Neutralizing antibodies could also play some role in assisting the clearance of latently infected cells. Barouch and colleagues showed that SHIV-infected monkeys infused with the potent neutralizing antibody PGT121 had very rapid falls in SHIV viremia and reduced levels of SHIV DNA.[23] A subset of these monkeys, particularly those with low levels of viremia prior to the infusions, controlled SHIV viremia without cART after the passively-infused antibody had been cleared. Hessell and colleagues have shown that the efficacy of anti-HIV neutralizing antibodies in preventing SHIV infection of monkeys is in part dependent on the ability of the antibodies to mediate antibody-dependent cellular cytotoxicity (ADCC), typically mediated via natural killer (NK) cells.[24] Infusions of antibodies that can also kill

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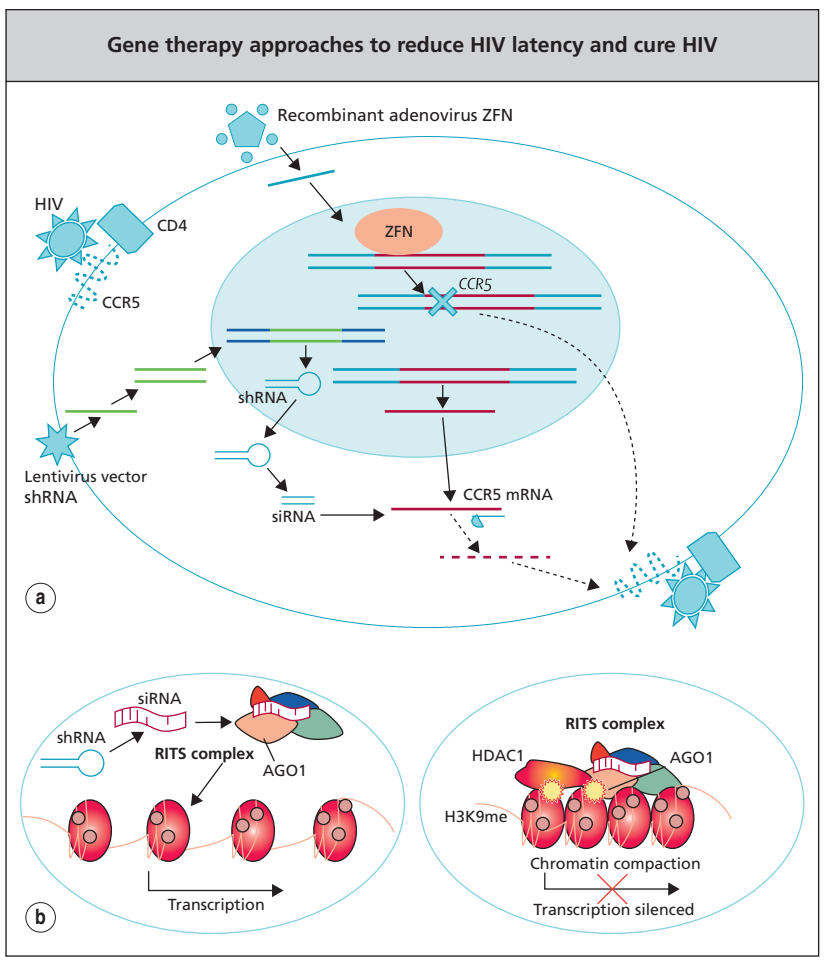

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Figure 105-4 Gene therapy approaches to reduce HIV latency and cure HIV. HIV usually enters cells by use of the CCR5 and CD4 co-receptors (a). Zinc-finger nucleases (ZFN) expressed by recombinant adenoviruses can block CCR5 gene expression, rendering the cell devoid of CCR5 and resistant to HIV. Alternatively, short-hairpin RNAs (shRNAs) expressed by lentivirus vectors can degrade CCR5 RNA, also rendering the cell devoid of CCR5 and resistant to HIV, through expression of a short interfering RNA (siRNA) that binds to the CCR5 messenger RNA (mRNA). Transcription of HIV is favoured by an open chromatin structure in the nucleus, shown by widely spaced histones (b, left). siRNA can bind to the RNA-induced transcriptional silencing (RITS) complex, which can result in chromatin compaction and silencing of HIV transcription (right), potentially leading to a permanent latent state for HIV in the cell. AGO1=argonaute RISC catalytic component 1; HDAC1=histone deacetylase 1; H3K9me=trimethylation of histone H3 at lysine 9. *(From Kent SJ,* et al.*: The search for an HIV cure: tackling latent infection.* Lancet Infect Dis *2013 Jul; 13(7):614-21.)*

HIV-infected cells (ADCC antibodies) should also help clear reactivated latently infected cells.

Gene Therapy Approaches to Cure HIV

p0120 Blocking the HIV co-receptor CCR5 is being studied in attempts to cure HIV. The cure of the Berlin patient administered a CCR5-defective BMT highlights the potential utility of this approach. About 1% of Caucasians are homozygous for a deletion in the *CCR5* gene that does not seem to be deleterious to their general health. These subjects who are homozygous for the common *CCR5*-deletion are naturally resistant to HIV, making CCR5 modulation an attractive target (Figure 105-4). Depletion of CCR5 expression is being attempted both through using short-hairpin RNA (shRNA) to degrade CCR5 mRNAs and through zinc-finger nucleases encoded by adenoviruses to block *CCR5* gene expression. This latter approach has been studied in a small series of subjects, with the level of reduction in CCR5 expression correlating with reduced levels of viremia off cART.[25] Wider clinical trials of these therapies with improved vectors are planned.

p0125 An alternate gene therapy approach is to enforce latency so that HIV cannot be reactivated using shRNAs that induce stable epigenetic changes in the integrated HIV DNA.[26] (Such approaches, while promising *in vitro*, are not yet in clinical trials.)

Conclusions

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p0130 There is considerable enthusiasm amongst the community and amongst many researchers for tackling approaches to cure HIV. Several paths towards reducing or clearing cells with latent HIV infection have been developed and are in various stages of clinical studies. The recent recrudescence of viremia in two subjects who received BMT and stopped cART as well as one baby treated very early with cART does, however, provide a salutary lesson regarding the enormity of the task. Insights gained into the biology and control of latent HIV may also provide useful pathways for future HIV treatments and vaccines. Intensive research on HIV cure strategies is likely to lead to novel therapies in the coming decade.

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