



Prevalent Chronic Infections Modulate T-Cell Phenotypes and Functions Enhancing HIV Susceptibility, Dissemination, and Persistence in African Population

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Abstract

While many studies have associated HIV prevalence with socio-economic status, few have explored the host's immunity status prior to HIV infection. High HIV prevalence in Africa may in part be contributed by a high prevalence of other persistent infections that modulate the host immunity towards phenotypes that promote HIV acquisition. In this narrative review, we examined how four most prevalent pathogens in Africa (human papillomavirus, herpesviruses, *Mycobacterium tuberculosis*, and helminth infections) modulate immunity to favor their survival and in turn, also influence HIV acquisition. We have described how these pathogens expand the number of memory and activated T cells, increase the expression of HIV entry receptors leading to an increased HIV susceptibility, and show how these pathogens' immunoevasive strategies may favor HIV persistence. A better understanding of the association between immunomodulation caused by other prevalent infections and HIV/AIDS prevalence may improve HIV/AIDS preventive strategies in Africa. We suggest intensifying efforts to control these chronic infections by making drugs or vaccines available in endemic regions. This may act as another indirect strategy to complement current HIV/AIDS interventions in Africa. We also call for more research to understand better the relationship between immunomodulation by other prevalent infections and HIV incidence.

Keywords: HIV prevalence; HIV persistence; Immune activation; HIV susceptibility; Immunomodulation

Introduction

HIV global prevalence

Despite 40 years of efforts towards ending the HIV epidemic, HIV remains a global health concern with over 39 million people worldwide estimated to be living with HIV in 2022, 66% of them living in Africa (UNAIDS, 2023). Eastern and Southern African populations remain disproportionately affected by HIV, accounting for over half of all people living with HIV (UNAIDS, 2023). Tanzania is amongst the Eastern African countries with high HIV prevalence (4.3%) whereby 1.7

million people, primarily adolescents and young adults between the age of 15-49 years, were estimated to be living with HIV by the year 2022 (UNAIDS, 2023). The reasons for the higher HIV burden in Africa are complex and include both socio-economic factors and medical factors, such as prevalence of other chronic infections that are common in the region, such as herpesviruses, HPV, *M. tuberculosis*, and helminths (Holmes et al., 2003; Sagna et al., 2010). Herpesviruses (e.g. cytomegalovirus (CMV), Herpes simplex viruses, Herpes zoster, Kaposi's Sarcoma-associated herpesvirus (KSHV)), HPV, *M.*

tuberculosis are HIV-associated opportunistic infections which are especially life-threatening in untreated individuals living with HIV while the role of different helminths in HIV disease progression is still controversial (Justiz Vaillant and Naik, 2022). These pathogens have also been associated with HIV risk (Smith-McCune et al., 2010; Auvert et al., 2011; Emery, 2015; Johnson et al., 2015), however, their mechanism of causing such a risk remains unclear. One possibility is that such infections might modulate immune pathways that may potentially influence HIV susceptibility, dissemination, and/or disease progression.

Herein, we will review how other chronic infections that are prevalent in Africa alter the host immune phenotypic and functional profile to in turn, favor HIV infection, dissemination and persistence. This review focuses on the following chronic infections: herpesviruses, HPV, helminths and *M. tuberculosis*.

Discussion

Immune cell phenotypes associated with HIV susceptibility and persistence

It is well-established that, HIV disease progression and mortality are linked to chronic inflammation and persistent immune activation (Giorgi et al., 1999; Hazenberg et al., 2000; Hazenberg et al., 2003; Deeks et al., 2004; Chachage and Geldmacher, 2014). Studies have shown that HIV-1 preferentially targets CD4 T cells with effector memory phenotype (Groot et al., 2006). Considering that most T cells with effector memory phenotype reside in the host tissues to provide immediate protection against invading pathogens or toxins, this suggests that they also provide an initial burst of HIV replication in the tissues when infected. On the other hand, tissue residing dendritic cells have been associated with the facilitation of HIV infection of CD4 T cells through shuttling of HIV to the secondary lymphoid organs where a majority of HIV replication and dissemination occurs (Izquierdo-Useros et al., 2007; Nasi et al., 2017; Crisci et al., 2019; Banga et al., 2023). Helper CD4 T cells

which can be infected by HIV in the secondary lymphoid organs are mainly memory cells that are known to express lymphoid homing receptors CCR7 and CD62L receptors as opposed to effector memory cells which lack these receptors (Sallusto et al., 2000; Groot et al., 2006; Lewis et al., 2008). Furthermore, HIV-infected CD4 T cells with a central memory phenotype have been considered as reservoirs of the virus which maintain viral persistence due to their homeostatic and antigen-driven proliferation property (Chomont et al., 2009; Banga et al., 2016). For these reasons, it is possible that people with a larger population of effector memory CD4 T cells in their tissues such as in the female genital mucosal tissues may be more susceptible to HIV infection than those with low numbers of these cells (Gupta et al., 2002; Groot et al., 2006; O'Neil et al., 2021). In addition, homeostatic maintenance and survival of memory T cell population require cytokines such as IL 2, IL 7 and IL 15 (Raeber et al., 2018). The presence of these cytokines in the peripheral could benefit HIV-infected CD4 memory T cells by maintaining and/or augmenting their survival leading to enhanced HIV persistence (Figure 1).

HIV preferentially targets and productively replicates in CD4 T cells that express the chemokine receptor CCR5 and integrin $\alpha 4\beta 7$ (Choe et al., 1996; Arthos et al., 2008; Nawaz et al., 2011; Joag et al., 2016; Tokarev et al., 2020). Furthermore, activated CD4 T cells (defined by their expression of HLA-DR and CD38) are susceptible to HIV infection (Koning et al., 2005; Begaud et al., 2006). Altogether, this shows the role of phenotype and function of CD4 T cells in influencing their susceptibility to HIV infection (Figure 1). Understanding how other prevalent persistent infections modulate the host immunity in the context of HIV is important as it may elucidate the association with HIV susceptibility, persistence, and disease progression in different populations.

Chronic infections associated with a permanent change in cell phenotypes

towards phenotypes that promote HIV acquisition.

(i). *Infection with latent herpesviruses*

Herpesviruses are DNA viruses that establish latency in various cells upon infection and stay for life in the host cells (Whitley, 1996; Cohen, 2020). Herpesviruses are ubiquitous in Africa with a prevalence of more than 90% in some populations compared to other continents such as Europe and the USA (Adjei et al., 2008; Cannon et al., 2010; Cesarman et al., 2019; Harfouche et al., 2019). During latency, the viruses especially cytomegalovirus (CMV) undergo several subclinical intermittent reactivation episodes which recruit more T cells into a memory pool and expand this population (Sylwester et al., 2005; Nikolich-Zugich, 2008). It has been shown in animal studies that CMV infection results into an expansion of memory T cells over time also known as memory inflation which leads to an expansion of the absolute number of T cells (Karrer et al., 2003). Cytomegalovirus infection has been regarded as another factor that may accelerate human T-cell aging (Koch et al., 2007). However, experiments in mouse model suggest infection with beta (CMV), gamma (murine herpesvirus-68) herpesviruses or combination of the two does not affect the survival or T cell responses to other unrelated viruses but could delay immunoglobulin class switch (Marandu et al., 2014; Marandu et al., 2015). A study by Smith et al showed an elevated immune activation of CD4 T cells specific for herpesviruses (CMV, Epstein Barr virus (EBV), Herpes simplex virus and or varicella zoster virus) assessed by the expression of CD38 and HLA-DR in HIV-infected individuals (Smith et al., 2013). *In vitro* stimulation of cord blood mononuclear cells (CBMCs) from CMV seronegative women with human CMV has been shown to upregulate the expression of CCR5 on CD3+CD4+ CBMCs (Emery, 2015; Johnson et al., 2015). The main conclusion from the mentioned study is that an increased expression of CCR5 on CD3+CD4+ CBMCs *in vivo* may facilitate in-utero HIV-1 transmission in women carrying latent CMV.

A recent study done in a high-risk population in coastal Kenya showed levels CMV specific antibody titers were not associated with HIV-1 acquisition (Fwambah et al., 2023). However, the study did not analyze T cell phenotypes prior to HIV exposure and had no CMV uninfected control group which both could lead to an effective conclusion regarding the immune modulation caused by CMV and the risk for HIV acquisition.

Moreover, an *ex vivo* study using human ectocervical tissue models showed that HSV-2 infection augments HIV-1 replication, and that was associated with elevated CD4, CD38, and CCR5 transcripts (Rollenhagen et al., 2014). HIV coinfection with herpesviruses is very common in Africa, since HIV's main target cells for infection are activated memory CD4 T cells expressing co-receptors CCR5 or CXCR4, co-infection with herpesviruses may be acting as fuel for HIV expansion and dissemination. Furthermore, herpesviruses have various strategies for evading the host immune system such as the downregulation of MHC, encoding MHC-I decoy, apoptosis inhibition, downregulation of CD107a on CD8 T cells, and production of anti-inflammatory cytokine homolog (Moore et al., 1990; Goldmacher, 2005; Brune, 2011; Fliss and Brune, 2012; Sin and Dittmer, 2012; Christensen-Quick et al., 2019; Broussard and Damania, 2020; Fletcher-Etherington et al., 2020). These strategies may favor HIV persistence in cases where a host is co-infected with HIV and one or a combination of the herpesviruses. Therefore, considering their effects on the host immunity such as immune aging, activation, and upregulation of receptors for HIV entrance, infection with herpesviruses may act as a key factor for increased HIV persistence, susceptibility, and disease progression.

(ii). *Infection with human papilloma viruses*

Human Papilloma Virus (HPV) is a non-enveloped DNA virus with a genome size of approximately 8kb. The virus is sexually transmitted and highly associated with anogenital cancer in both women and men. Once the virus enters the host it may be

cleared by the host's immunity or stay latent in the host tissues (Frazer, 2009; Shanmugasundaram and You, 2017). The global data indicate that HPV infection and disease are more prevalent in developing countries especially in eastern and southern Africa (42% and 32%, respectively) than in developed countries (23%) (Forman et al., 2012; De Vuyst et al., 2013; Kombe Kombe et al., 2020; Sung et al., 2021). There are two groups of HPVs that are categorized into high and low-risk HPV. The two well-studied and most prevalent high-risk (HR) strains are HPV 16 and 18 which accounts for 70% of cervical cancers in women worldwide (de Sanjose et al., 2010). Other HR-HPV types include HPV 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 70. Whereas, the most prevalent low-risk HPV are HPV 6 and 11, while others include HPV 42, 43, and 44 (Burd, 2003). Although the low-risk strains may not cause any disease, their interaction with the host immunity may significantly affect overall immunity to other pathogens. Due to their pervasiveness especially in Africa, research on HPV interaction with the host immune system and how they affect immunity against other infections is of paramount importance. For instance, HPV infection has been linked to an increased risk of HIV acquisition (Smith-McCune et al., 2010; Auvert et al., 2011; Houlihan et al., 2012; Liebenberg et al., 2019; Liu et al., 2022). The mechanism for this is largely unknown, however, a recent study has implicated HPV infection with alteration of the innate immune responses that may favor host susceptibility to HIV infection (Britto et al., 2020). Likewise, cell adhesion markers associated with maintaining the integrity of the mucosal membrane (occludin1, ZO-1, claudins 1, 2, 4 and E-cadherin) were downregulated in HPV-positive individuals suggesting an increased HIV access to CD4 T cells beneath the epithelial mucosal tissue. Although data from this study did not show that HPV significantly activates CD4 T cells, results from another recent study with a bigger sample size showed a significantly high frequency of activated CD4 T cells in the cervical mucosal cells from HPV-infected

women (Britto et al., 2020; Mbuya et al., 2020). However, data from both studies show no profound increase in the frequency of CD4 T cells expressing the well-known HIV susceptibility markers (CCR5 and $\alpha 4\beta 7$) in HPV-infected women. Interestingly they both showed that HPV infection alters host immunity towards susceptibility to HIV infection by either decreasing the expression of TLRs that recognize RNA (TLR3/7 and MDA5 mRNAs) or upregulating the expression of activation marker HLA-DR on CD4 T cells. On that account, future studies should further look into which immune cell pathways are modulated by HPV resulting in an increased HIV susceptibility of the host.

(iii). Infection with helminths

Over one billion people are hosting one or more helminth species with resource-limited countries in Africa, the Americas, and Asia bearing the most burden (WHO, 2012). Soil-transmitted nematodes are leading in global prevalence with more than 1.5 billion people infected followed by filarial nematodes (*Wuchereria bancrofti*, *Brugia malayi*) and platyhelminth flukes (*Schistosoma haematobium*, *Schistosoma mansoni*) carried by more than 200 million people of which majority are from low and middle-income countries including Africa, where HIV is also co-prevalent (Hotez et al., 2008; WHO, 2020; Ahmed, 2023). Since most of the helminths cause chronic infections, the host immune system is persistently being activated, which may give protection against immune-mediated diseases (Elliott and Weinstock, 2012; Weinstock and Elliott, 2014; Bhoj et al., 2022). Generally, helminths have been known to modulate host immunity by upregulating Th2 (characterized by the expression of Th2 anti-helminthic cytokines: IL-4, IL-5, and IL-13) and downregulating Th1 responses (reviewed in (Gazzinelli-Guimaraes and Nutman, 2018; Yegorov et al., 2019b; Li et al., 2020). Moreover, chronic helminth infections induce regulatory T cell (T regs) responses characterized by anti-regulatory cytokine IL-10 (Metenou et al., 2010; Metenou and Nutman, 2013). Although a direct association between Tregs and HIV

acquisition is yet to be determined, Tregs (CD25+FoxP3+ CD4 T cells) were shown to be frequent targets of HIV, further highlighting the potential role of helminth-induced Tregs in driving HIV infection (Chachage et al., 2016). More pieces of evidence continue to emerge from several studies elucidating how different helminth species dysregulate the immune system in a way that can even favor the establishment of other infections such as HIV. Schistosomiasis especially with *S. haematobium* significantly increases the risk of HIV infection in African women by up to over 2.5-fold (Kjetland et al., 2006; Downs et al., 2011; Downs et al., 2012; Wall et al., 2018). However, it has not been extensively explored whether the observed increased HIV risk by Schistosome infections is due to their induced tissue injury or T cell modulations (upregulation of Tregs, T cells activation and differentiation). A recent study has eloquently shown that *S. mansoni* suppresses type I interferon antiviral responses leading to an enhancement in HIV entry into cervical and blood CD4 T cells. Furthermore, they showed *S. mansoni* egg-positive individuals had increased mucosal homing integrin ($\alpha 4\beta 7$) expression on peripheral CD4 T cells which may favor HIV susceptibility (Yegorov et al., 2019a). *S. mansoni* has also been associated with low cytotoxic potential of HIV-specific CD8 T cells, suggesting a potential mechanism for enhancing HIV persistence (Obuku et al., 2023). Similarly, Kroidl et al. have demonstrated an increased risk of acquiring HIV in people infected with the causative agent of lymphatic filariasis, *W. bancrofti* (Kroidl et al., 2016), a nematode that lives in the host blood and lymphatic system but does not affect the genital area. Of note, chronic infections with *W. bancrofti* and other helminth species such as *Trichuris trichiura* and *Ascaris lumbricoides* increase the proportion of activated T cells that express receptors which may enhance HIV susceptibilities such as CCR5 and/or CD38 and HLA-DR (Kalinkovich et al., 1998; Chachage and Geldmacher, 2014; Chachage et al., 2014; Kroidl et al., 2019). Chronic infection with *W. bancrofti* has also been

associated with an increased frequency of CD4 T cells with effector memory phenotype (CD27 negative CD45RO positive) (Kroidl et al., 2019). All these phenotype changes on T cells are associated with enhanced susceptibility to HIV infection or if a host is co-infected may exacerbate HIV disease progression since immune activation is the hallmark of HIV disease progression (Giorgi et al., 1999; Hazenberg et al., 2003; Hunt et al., 2003; Koning et al., 2005; Begaud et al., 2006; Card et al., 2009). To support that, studies have shown that community-based anthelmintic treatment is associated with a decrease in plasma HIV load and improved CD4 T cell count (Walson et al., 2008; Walson et al., 2009; Weisman et al., 2017). Therefore, further research is needed to determine whether the mass administration of anthelmintic drugs that have been ongoing since the 2000s has resulted in a reduction in HIV incidence in helminth and HIV-endemic areas.

(iv). Infection with latent *Mycobacterium tuberculosis*

Tuberculosis (TB) is an ancient, preventable, and treatable disease that is the second leading global cause of death due to a single infectious agent after COVID-19 (WHO, 2023). In 2022 alone, newly diagnosed TB cases globally were 7.5 million people (WHO, 2023). Moreover, about 25% of the world's population is infected with *Mycobacterium tuberculosis* (Mtb) in a latent/dormant form (Houben and Dodd, 2016). People carrying Mtb have a 5–10% lifetime risk of developing active TB while the risk is greater in people with HIV, malnutrition, diabetes, or tobacco users (Vynnycky and Fine, 2000). Africa is the second leading region with the most TB cases accounting for 23% of all reported cases in 2022 (WHO, 2023). Of note, HIV-driven TB is highest in Southern Africa, with more than 50% of people with active TB known to concurrently be living with HIV (WHO, 2023). It is well documented that HIV impairs Mtb-specific CD4 T cells, leading to increased susceptibility to TB (reviewed in (Saharia and Koup, 2013)). This may be

favored by increased expression of CCR5 and production of IL-2 on/by Mtb-specific CD4 T cells of people with latent or active TB upon HIV engagement, thereby supporting the HIV entry and replication, and in turn, resulting in a rapid depletion of functional CD4 T cell responses (Geldmacher et al., 2008; Geldmacher et al., 2010). Thus, early depletion of these cells which are essential in the control of Mtb infection following an HIV infection in part contributes to the increased risk of TB disease and simultaneously accelerates HIV progression to AIDS in HIV-Mtb co-infected individuals. Antiretroviral therapy reduces the risk for TB disease in people with HIV, however, not to a level observed in HIV-uninfected individuals, possibly due to the inability of ART to completely restore Mtb-specific T cell responses (Schluger et al., 2002; Sutherland et al., 2006).

Not much is known about the risk of acquiring HIV in people with latent or active TB infection, but few reports show that individuals infected with active Mtb have an elevated fraction of HLA-DR on Mtb-specific CD4 T cells compared to those with latent Mtb (Luo et al., 2021). However, the overall frequency of activated CD4 and CD8 T cells (CD38+ HLA-DR+) is increased in both latent and active Mtb infection. Furthermore, a recent study has shown that HIV replication is more efficient in CD4 T cells collected from latent Mtb-infected donors (He et al.,

2020). These new findings suggest that systemic inflammatory cytokines released due to latent Mtb infection may in addition lead to activation of HIV-1 transcription as already described by other studies (Zhang et al., 1995; Garrait et al., 1997).

Higher levels of CCR5 expression on monocyte-derived and alveolar macrophages after *in vivo* and *in vitro* Mtb infection has previously been reported (Fraziano et al., 1999). Since HIV can easily infect these cells due to an enhanced expression of CCR5 and also their ability to resist cytopathic effects after HIV infection, Mtb infection may lead to an enhancement of both HIV susceptibility and persistence. In summary, the immunological cost for harboring latent Mtb in the host has not been intensively explored, especially with the published facts that this microbe is responsible for persistent immune activation. More studies are needed to determine whether by eradicating or lowering Mtb prevalence will reverse these immune alterations caused by Mtb infections and result in better control of HIV/AIDS in the population.

In summary, infection by herpesviruses, HPV, helminths and Mtb modulates the host immunity toward an increased risk for HIV acquisition and persistence. These modulations are mostly on the cell phenotypes such as upregulation or downregulation of markers and cytokines associated with an increased HIV susceptibility or persistence (Figure 1).

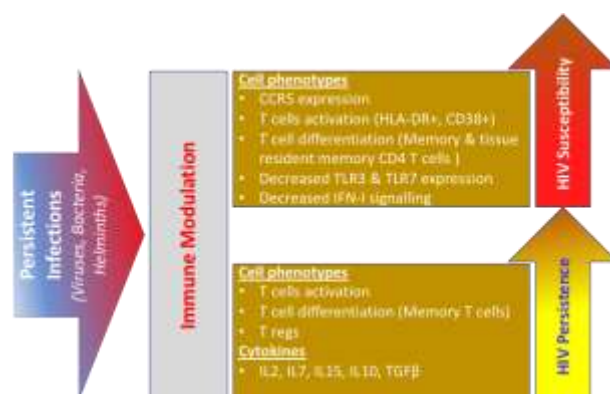


Figure 1: Immune modulation by persistent pathogens.

Conclusions

HIV/AIDS control and prevention strategies require a multidisciplinary approach that includes understanding the host immunity's prior status. Most populations living in Africa harbor other prevalent persistent infections. Unfortunately, the cost of harboring these infections to host immunity and potential impact on HIV susceptibility, dissemination and persistence has not been described in depth. We have

looked at some of these pathogens and how they affect the host immunity in a way that may explain the high prevalence of HIV/AIDS in Africa. The major pathogens that this review focused on are; herpesviruses, human papilloma viruses, helminths, and Mtb, all of which are common in Africa and have been previously described to alter the host immunity in different ways as summarized below (Figure 2).

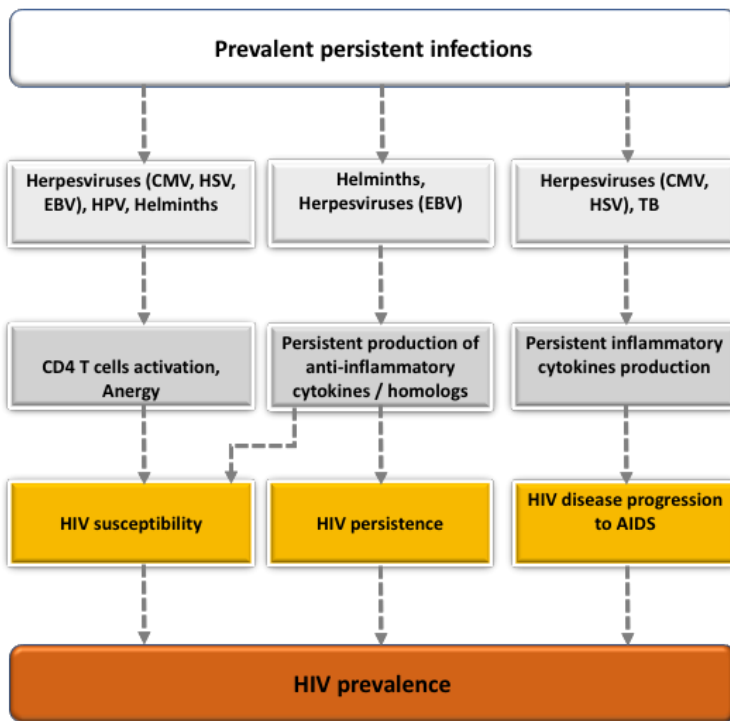


Figure 2: A summary chart suggesting how prevalent infections may modulate the host's immune system, leading to an increased HIV prevalence.

Specifically, we have described how HPV, herpesviruses, Mtb, and helminth infections expand the number of memory and activated T cells, and increase the expression of HIV entry receptors leading to an increased HIV susceptibility. We also discussed how these pathogens' immunoevasive strategies may lead to HIV persistence. Based on the reviewed data, we suggest that eliminating or controlling these infections by making drugs or vaccines widely available may act as another indirect strategy to complement the existing ones which are directed toward

fighting HIV/AIDS in African populations. However, we also show the knowledge gap in (1) the identification of immune pathways that are critical for HIV acquisition and persistence that are modulated by the reviewed pathogens and (2) population data that have confirmed the reduction of HIV incidence, especially in areas where interventions to eliminate helminth infections have taken place. We therefore, call for more research to better understand the association between immunomodulation caused by other prevalent infections and HIV incidence as

these may improve HIV/AIDS control strategies in Africa.

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List of Abbreviations

AIDS – Acquired Immunodeficiency Syndrome
CMV – Cytomegalovirus
EBV – Epstein Barr Virus
HSV – Herpes Simplex Virus
HIV- Human Immunodeficiency Virus
HPV – Human Papilloma Virus
Mtb – *Mycobacterium tuberculosis*

Ethics Approval

Not applicable

Competing Interests

The authors declare they have no competing interest

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Authors' Contributions

TFM conceived the idea. Both TFM and MSC contributed equally in drafting the manuscript, critically reviewing the contents, and approving the final version of this manuscript.

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