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The Detection and Management of Early HIV Infection: A Clinical and Public Health Emergency

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Abstract

This review considers the detection and management of early HIV infection (EHI), defined here as the first 6 months of infection. This phase is clinically important because a reservoir of infected cells formed in the individual renders HIV incurable, and the magnitude of viremia at the end of this period predicts the natural history of disease. Epidemiologically, it is critical because the very high viral load that typically accompanies early infection also makes infected individuals maximally contagious to their sexual partners. Future efforts to prevent HIV transmission with expanded testing and treatment may be compromised by elevated transmission risk earlier in the course of HIV infection, although the extent of this impact is yet unknown. Treatment as prevention efforts will nevertheless need to develop strategies to address testing, linkage to care, and treatment of EHI. Cost-effective and efficient identification of more persons with early HIV will depend on advancements in diagnostic technology and strengthened symptom-based screening strategies. Treatment for persons with EHI must balance individual health benefits and reduction of the risk of onward viral transmission. An increasing body of evidence supports the use of immediate antiretroviral therapy to treat EHI to maintain CD4 count and functionality, limit the size of the HIV reservoir, and reduce the risk of onward viral transmission. Although we can anticipate considerable challenges in identifying and linking to care persons in the earliest phases of HIV infection, there are many reasons to pursue this strategy.

Keywords

early/acute HIV infection; HIV transmission; treatment as prevention; antiretroviral therapy

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INTRODUCTION

The goals of immediate antiretroviral therapy (ART) for individuals presenting with early HIV infection (EHI) are twofold: first, for the health benefits of the individual and second to reduce the risk of onward viral transmission. Use of ART to control the HIV epidemic has garnered considerable interest at the population level. The extent to which elevated transmission during EHI[1]—if not reached by treatment—might compromise the preventive effect is a matter of debate.[2–5]

The evidence to date about the feasibility of treatment as prevention targeting persons with EHI are summarized in Table 1. This review synthesizes the existing evidence on the individual-level effects of early treatment and its potential role in using ART to prevent HIV transmission. Specifically, we consider the significance of early treatment in 3 areas: the challenges of finding early infection, in moderating essential behavior change in these individuals, and considerations for treatment of those with EHI.

EARLY HIV INFECTION

Sexual transmission of HIV generally involves only 1 or a small number of viral variants infecting receptive cells.[6,7] The earliest days of infection are marked by HIV replication in the mucosa, submucosa, and lymphoreticular tissues, during which viral markers can only be detected in the affected tissues but not in the plasma.[8] Once HIV RNA concentration increases to 1–5 copies per milliliter in plasma, nucleic acid amplification can be used to qualitatively detect HIV, after which the sequential appearance of various viral makers define the stages of EHI for which different quantitative clinical assays can be used to monitor viral load.[9] At the same time, the initial immune response includes a “cytokine storm” that in a substantial number of newly infected people produces acute retroviral syndrome[10] and that can be used to mark the stages of acute infection.[11]

Gut T-cell depletion[12] and rapid growth in the HIV DNA reservoir size[13,14] take place in the earliest (first ~25 days) after infection.[15] However, elevated risk of transmissions has been shown to persist for up to 6 months after seroconversion.[16] “Early HIV infection” here will therefore refer to all stages of acute infection including seroconversion and up until the establishment of early chronic infection, approximately 3–6 months after HIV acquisition.

This stage of infection is critical both clinically and epidemiologically because (1) the reservoir of infected cells is formed in the individual that render HIV incurable; (2) the magnitude of viremia at set point predicts the natural history of disease,[17] and (3) the very high viral load that typically accompanies acute infection—combined with specific characteristics of recently transmitted viral variants[18]—can make acutely infected individuals maximally contagious to their sexual partners.[9]

HIV AND THE SPREAD OF INFECTION

The biological plausibility of elevated HIV transmission risk during EHI is based on the heightened viral load of persons with early infection—often on the order of 10^6 log copies

per milliliter[19]—which is also mirrored in high levels of virus in the genital tract.[19–21] In addition, characteristics of the transmitted virus,[18] concomitant sexually transmitted infections,[22] and patterns of sexual behavior among recently infected individuals[23] who may be unaware of their status[24] may all factor into the role that EHI plays in the spread of HIV. However, the extent to which HIV treatment as prevention programs must account for transmission during EHI is a matter of some debate.[5,25]

The biological plausibility that EHI may enhance transmission risk is supported in some risk groups by the findings of phylogenetic methods to define transmission clusters[22,26–28] or reconstruct transmission events during EHI[29] using viral sequences from recently infected persons. Results suggest that HIV transmission from persons with EHI may account for 25%–50% of all viral transmissions within certain populations.[16,26,29] Some posit, however, that the failure of these methods to consider other risk factors for transmission or to distinguish between new and chronic infection may lead them to overestimate the portion of new infections attributable to EHI.[30]

Mathematical models also provide insight into the role of EHI in HIV epidemiology. As we have summarized previously,[9,31] model estimates of the contribution of EHI to population-level transmission have varied widely, with estimates of the portion of new cases attributable to EHI ranging from 1% to 82% (Table 2), depending on epidemic stage, model structure, assumptions about sexual contact rates and patterns, and the assumed duration of high infectiousness associated with EHI. We are aware of only one model to date that has formally assessed the potential impact of prevention interventions during EHI,[25] the results of which suggest that transmission prevention during both EHI and chronic infection are needed for maximal impact.

IDENTIFYING EHI

Successful use of ART during EHI to control the HIV epidemic will depend greatly on our ability to effectively screen and identify these individuals to target for intervention, although this is not yet part of routine testing strategies. Such efforts will likely demand more frequent testing, particularly among those believed to be at greater risk of HIV infection and with the use of novel tools such as self-administered HIV tests—where legally sanctioned[47]—paired with open access to care. The acute phase of EHI when antibodies are not yet present will remain undetected by traditional antibody tests,[48–50] when diagnosis must rely on direct detection of virus using nucleic acid amplification tests or viral antigen such as p24. Give the financial, technical, and logistical barriers to widespread use of nucleic acid amplification tests, third- and fourth-generation indirect enzyme immunoassays have emerged as a strong alternative. The sensitivity of these tests to HIV antibody isotypes that emerge earlier in the course of infection (IgM and IgG), and in the case of fourth generation to p24 antigen, allow detection earlier in the course of infection with relatively good sensitivity.[3–5,49,51] However, limited availability of fourth-generation enzyme immunoassays in resource poor settings and low sensitivity for detecting HIV infection before seroconversion limits their utility in many settings with high EHI prevalence.[52,53]

Pooling samples for batched RNA screening may be a cost-effective alternative for EHI detection in places with higher prevalence of persons with EHI,[6,7,49,54–58] but laboratory-based assays remain costly, necessitate people attending for testing venipuncture, and require patient follow-up. Field evaluations of available point-of-care tests to date have reported disappointingly high false-positive and false-negative rates.[1,9,59,60]

In light of these shortcomings, symptom-based screening—particularly those that incorporate targeted screening—must be developed as a cornerstone of field efforts to identify persons with EHI. Candidate populations include those presenting with symptoms indicative of sexually transmitted infections[2–5,61,62] or with reported high-risk behavior.[6,7,11,50,62] A strengthened symptom-based screening strategy will also require retraining of clinicians and community health workers, paired with routinized point-of-care viral load testing.[63]

PREVENTION IN PERSONS WITH EHI

Beyond the limitations of timely and adequate identification of acutely infected individuals are the unique challenges of preventing the HIV transmission in these individuals. Behavioral interventions will demand swift and decisive strategies to reduce risk behaviors, including notification of current sexual partners, limitation of new partner acquisition, condom use, and, possibly, abstinence during the acute phase. Seeking behavior change is the most constant theme in HIV prevention, but the limited evidence available on behavior change during EHI[9,64,65] bode less well for future interventions in persons with EHI.

Following the biological plausibility of reduced viremia leading to reduced HIV transmission risk,[66,67] we expect that treated persons with EHI will be less likely to transmit to their partners. In the absence of a mechanism to directly observe this effect, the phylogenetic cluster study by Rieder et al on transmission dynamics in gay men in Switzerland suggests that at least 5 reconstructed transmission events were attributable to presumed transmitters who ceased early therapy.[68] Although discouraging from a disease control standpoint, these findings also underscore the need for new ways to modify and measure the impact of early ART on HIV transmission in persons with EHI.

THERAPEUTIC EFFECTS OF EARLY ART

The rationale for treating individuals with EHI is based on the suppressive effect of ART on patient viral load, which consistent of 4 elements: (1) alleviation of symptoms of early infection, (2) preservation of immune function, (3) reduction in the viral reservoirs, and (4) reduction of HIV transmission during EHI.

Until more recent evidence to the contrary,[15,69] early exposure to ART was considered something best avoided or at least be administered intermittently so as to minimize cumulative side effects or the development of drug resistance.[16,70] Here, we summarize findings from the body of literature reporting treatment effects of ART—defined as 1 to 4 antiretroviral drugs in a regimen—administered as either consistent or intermittent courses —during all phases of EHI (Table 3).

Early ART Alleviates Acute Syndrome Symptoms

Acute retroviral syndrome can manifest within days to weeks after exposure, as mildly as a viral syndrome or as severely as multisystem dysfunction.[18,116–118] By reducing viral levels in treated patients, ART can modify both the direct viral effect and the host immune response to the virus, thereby alleviating symptoms of acute infection.[9,27,68,96] Treatment for the sole purpose of reducing these symptoms was included as an indication for treatment for individuals with EHI in a recent set of treatment guidelines in the United Kingdom.[63]

Effect of ART in EHI on Immune Function

There is little debate about the role of immediate ART for individuals presenting with very low initial CD4 counts or who are severely unwell,[19–21,119] but there is some uncertainty about appropriate courses for those identified in EHI with only minor symptoms and high CD4 counts. Known immunological benefits of ART initiated during EHI to date fall into 2 general categories: slower disease progression and near-term improvements in HIV-specific immunological responses.

Regarding disease progression, numerous observational studies and 7 randomized clinical trials have identified associations between early ART and the slowing of the depletion of $CD4^+$ T cells[77,83–86,90–92,99,102,106,107] as well as with the facilitation of immune cell restoration.[22,80,92,94] Preservation of immune cell function has also been reported[23,95,100,108,112] but not universally.[24,115] In many of these studies, ART exposure was very brief and longitudinal follow-up time relatively short, limiting the strength of inferences that can be drawn about early treatment.

ART during EHI has also been associated with improved HIV-specific T-cell function,[5,25,73,89,96,100,110] although starting ART too early may possibly interfere with the initial HIV-specific humoral response.[115] Persistent immune activation has been identified among early ART initiators,[29,75,81,112,113] possibly to a lesser extent than persons starting ART during chronic infection.[16,26,29,88]

Taken together, these data suggest that immediate use of ART irrespective of CD4 count could be expected to confer health benefits to patients with HIV. However, the durability and magnitude of these effects are yet unknown, limiting their immediate application to clinical decisions regarding optimal management of persons with EHI. Future research efforts must take note that increasingly higher CD4 thresholds for ART initiation in guidelines will continue to narrow the gap between early and delayed therapy, necessarily limiting our ability to decisively attribute observed health effects to early therapy.[30,48–50,95]

Effect of ART in EHI on Virological Outcomes

In addition to improvements in surrogate markers of clinical progression, studies report potential benefits of ART during EHI on virological outcomes. The potential effect of ART on the viral set point—the level at which a patient's viral load stabilizes after seroconversion—is of great interest given its strong association with the course of disease progression.[120] Two observational studies[101,109] and several trials[83,87,104] have examined this issue, all but one[101] reporting lower viral set points among patients treated during EHI versus those who

were not. The variable definitions of viral set point across these studies, defined as the viral load at points in time ranging from 7 to 72 weeks after ART cessation, and the noncomparability of controls may contribute to the inconsistency of results across observational studies.[87,104,109] Nevertheless, the fact that 3 randomized clinical trials[87,104,107] all demonstrated some reduction in viral set point between ART-treated and control participants suggest the presence of a substantive effect.

Although some report no effect of transient therapy on virological indicators after cessation,[92,101,113] most identify a significant difference in the viral loads of the early treatment groups[74,77,80,84,95,96,99,107,110,114] versus their comparators. Interruption of ART almost invariably leads to the reemergence of detectable viral replication and the progression of HIV infection, a result of the establishment of inaccessible viral reservoirs.[121]

Finally, very early treatment may impact the size of the latent reservoir that is established early after infection. Research in this area may be critical for future work on HIV cure,[71,105] the key barrier to which is eradication of the latent pool of inaccessible reservoir cells.[122] To date, results of 4 separate study groups provide the most insight. The RV254/SEARCH 010 Study Group has reported that ART during EHI may play a key role in immune restoration and preventing the seeding of the HIV reservoir in the gut mucosal tissue of 20 Thai participants.[15] These findings are supported by other groups who also report reduction in the sizes of viral reservoirs—measured as levels of cell-associated HIV DNA—among individuals with EHI receiving immediate ART compared with deferred therapy,[75,85,88,123] in some cases even to levels comparable with those of documented elite controllers.[124] Examining perhaps the most rigorous measure of the persistent HIV reservoir, resting CD4 cell infection with replication competent virus, Archin et al observed a strong correlation between the extent of viral replication before suppressive ART and the size of the resting cell reservoir.[71] The Virological and Immunological Studies in Controllers after Treatment Interruption group demonstrated that early ART could also enhance viral control of therapy irrespective of HLA type and CCR5 genotype in a subset of patients treated intermittently during early infection.[72,81,125] This group showed that immediate ART initiated within 12 weeks of diagnosis and maintained for a minimum of 3.5 years before discontinuing was associated with a higher proportion of viral controllers several years after stopping ART compared with the proportion of controllers described in untreated chronic infection (from <1% to 15.6%).

These findings together with the successful elimination of HIV from 1 patient[126] and the functional cure reported in an infant treated at birth[127] give cautious hope to the concept of strategic use of ART to limit establishment or reestablishment of the viral reservoir and work toward HIV cure.

Other Considerations of Early ART

A successful strategy to carry out early ART for prevention purposes must address a complex interplay of factors likely to mediate its impact. The acceptability of such a strategy must, for example, help patients faithfully confront the reality of lifelong adherence from an earlier stage in the course of disease, with which we have limited experience. Our

understanding of the toxicity of prolonged exposure to antivirals for even longer duration is also limited.[86]

The choice of ART regimens will also determine the success of treatment as prevention strategies targeting persons with EHI. Current regimens are designed for simplicity, reduced cost, tolerance, patient and clinician preference, and the genotype of transmitted virus. However, for persons with EHI, treatment choices may be informed by patients' desires to initiate therapy as soon as possible—often before resistance data are available—and the inclusion of agents known to achieve rapid decreases in plasma viral load. Selecting drugs that concentrate in the genital or gastrointestinal tracts, such as integrase inhibitors, may protect lymphocytes in these compartments that are especially vulnerable to the adverse effects of EHI and also present clear prevention advantages. Evidence that intensive drug regimens of up to 5 agents may confer benefit over standard triple therapy for individuals with EHI is still formative.[96]

The potential risks of earlier initiation of ART can be, in part, anticipated, given the anticipated risks of lifelong treatment for all patients with HIV. Early ART may present new challenges for effective delivery of patient care, but may also have positive impacts on patient quality of life[82] and retention in care.[128] But the relatively short follow-up periods, transient nature of the treatment exposure, and small sample sizes limit insight and underscore the need for further research into comparative treatment outcomes.[129] Furthermore, interruption of therapy has been associated with major cardiovascular, renal, and hepatitic disease,[69] outcomes that must be considered when bearing risks versus benefits of sustained therapy.

Finally, as with all treatment as prevention efforts, feasibility of future programs must anticipate logistical challenges such as drug stock-outs or unavailability of second-line regimens.[130]

SUMMARY AND CONCLUSIONS

The formative nature of research into ART during EHI is reflected in the lack of consensus surrounding treatment guidelines for these persons. The United States and United Kingdom are the only 2 countries known to date with specific guidelines for clinical management of disease in persons with EHI.[63,130–132] In both cases, treatment is recommended, though both note caveats about the strength of evidence.

However, an increasing body of evidence supports the role of immediate ART among individuals identified with EHI to facilitate immune function, limit the size of the HIV reservoir, and reduce the risk of onward viral transmission. We and others have anticipated the considerable difficulty in finding subjects in the earliest phases of HIV infection given the added demands of repeat HIV testing, limitations of detection using currently available technologies, and the need for enhanced provider and patient awareness of the clinical and prevention significance of EHI. These considerations notwithstanding, future HIV control efforts will need to emphasize novel and targeted methods to identify patients with EHI and provide unequivocal support for treatment to improve their quality of life and limit onward transmission of HIV.

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TABLE 1

Evidence to Date on the Feasibility of Treatment as Prevention Targeting Persons With EHI

Things for Which There Is Some Evidence	Unknowns
ART at CD4 > 350 cells/mL reduces infectiousness by 96% in stable serodiscordant couples	How well ART can reduce infectiousness in persons with EHI, particularly in the preseroconversion phase
The extent to which EHI may contribute to ongoing transmission	How likely we are to be able to identify and treat a large enough portion of EHI to impact the efficacy of treatment as prevention within a population
Early ART can suppress viral load in individuals with EHI	The long-term safety of early ART, and the durability of the suppressive effect
Some regimens may be more effective at reducing viral load	The tolerability (toxicity) and the long-term safety of these regimens, although this may not be significantly different from those affecting the general population starting ART in chronic infection
Early ART has some short-term health benefits for the individual	Long-term health benefits of early ART for the individual
Adherence to short course is generally good	Feasibility of good adherence in the event of uninterrupted therapy
Resource poor areas have limited capacity to screen acutes or to provide routine viral load testing	The extent to which new technologies will be able to overcome these constraints

TABLE 2

Proportion of New Infection Attributed to Early EHI

Author	Population/Setting	Proportion of New Infections Attributed to EHI (%)
Jacquez et al[32]	MSM (United States)	25 to 51
Pinkerton and Abramson[33]	MSM (United States)	25 to 90*
Koopman et al[34]	MSM (United States)	20 to 47*
Kretzschmar and Dietz[35]	Hypothetical (United States)	65 to 82*‡
Coutinho et al[36]	Mixed	2 to 89
Xiridou et al[37]	MSM (Europe)	<1 to 39
Pinkerton[38]	Mixed (United States)	3 to 17
Prabhu et al[39]	Mixed (United States)	11
Goodreau et al[40]	Heterosexuals (SSA)	20 to 25
Hayes and White[41]	Heterosexuals (SSA)	23 to 41†
Eaton et al[42]	Heterosexuals (SSA)	16 to 28*
Pinkerton[43]	Heterosexuals (SSA)	85 to 93†
Abu-Raddad and Longini[44]	Heterosexuals (SSA)	~7 to ~15‡
Salomon and Hogan[45]	Heterosexuals (SSA)	~20 to 40†
Hollingsworth et al[46]	Heterosexuals (SSA)	9 to 31
Powers et al[25]	Heterosexuals (SSA)	19 to 52‡

MSM, men who have sex with men; SSA, sub-Saharan Africa.

*Transmission probabilities were drawn from the listed population, but the reported proportion of new infections attributed to EHI result from a range of hypothetical sexual behavior parameters that do not necessarily reflect those of the same subpopulation.

†Range of estimates reflect the estimated proportion of transmissions during an HIV infected person's entire infectious period that occur during EHI. The extent to which this proportion corresponds with the proportion of all transmissions that occur during EHI at the population level will depend on the epidemic phase and sexual contact patterns.

‡The range of estimates shown was extracted from the endemic-phase portion of graphs showing the time-course of the proportion due to EHI.

TABLE 3

Summary of Studies of the Virological or Immunological Effects of ART Administered During EHI (≤6 Months After Seroconversion)

Author	Setting	Cohort Name/Study Design	N	Comparator Group
Ananworanich et al[15]	Asia	Open-label treatment 2-arm trial	30	15 HIV+ ART naive
Archin et al[71]	NA	CHAVI/STAT	27	—
Bacchus et al[72]	ER	VISCOTI	12 (all control HIV after interruption)	—
Cellerai et al[73]	ER	Retrospective clinical	20	15 HIV+ ART naive long-term nonprogressors
Desquilbet et al[74]	ER	PRIMO (SERECO controls)	58	116 HIV+ ART naive
Evering et al[75]	NA	Clinical	3	2
Fidler et al[76]	ER	Clinical	79	—
Fidler et al[77]	ER	Clinical (CASCADE controls)	89	179 HIV+ ART naive
Gay et al[78]	NA	UNC Duke Acute HIV Infection Consortium	51	92 HIV+ ART naive
Gianella et al[79]	ER	Clinical (Swiss HIV Cohort Study controls)	32	89 HIV+ ART naive with recent EDI
Goujard et al[80]	ER	RCT: ANRS-112 INTERPRIM 3-arm Trial	30: ART; 31: ART-STI; 30: ART-STI-IFN	—
Goujard et al[81]	ER	ANRS PRIMO	164	—
Grijsen et al[82]	ER	PRIMO-SHM substudy	84	28 HIV+ ART naive
Grijsen et al[83]	ER	RCT: PRIMO-SHM 3-arm trial	38: 24 wk cART 38: 60 wk cART	36: no (deferred) ART
Hecht et al[84]	NA	AIEDRP cohort	13 acute 45 early	337 HIV+ ART naive
Hocquelox et al[85]	ER	Retrospective clinical	32	—
Hoen et al[86]	ER, NA	QUEST GW	148	—
Hogan et al[87]	NA	RCT: ACTG 5217 (set point)	66	63: no (deferred) ART
Jain et al[88]	NA	UCSF Options Project	32	34 HIV+, ART initiated later (unknown N of HIV − controls)
Jansen et al[89]	ER	Clinical	11	6 HIV+ ART naive
Kaufman et al[90]	NA	Single-arm open-label	14	—
Kinloch-de Loes et al and Koegl et al[91,92]	ER	RCT	39	38: placebo
Koegl et al[92]	ER	Clinical AHI/PHI cohorts	100	56 HIV+ ART naive
Lampe et al[93]	ER	QUEST (CASCADE controls)	79	358 HIV+ ART naive
Le et al[94]	NA	San Diego Primary Infection Cohort	213	136 HIV+ ART naive
Lodi et al[95]	ER, NA, AUS	CASCADE	m	—
Markowitz et al[96]	NA	Clinical	16 (11 of whom also part of a vaccine trial)	—
Mehandru et al[97]	NA	Clinical	54	18 uninfected controls
Moir et al[98]	NA	Clinical	43: early 50:chronic	35 HIV−
Niu et al[99]	NA	RCT: DAIDS Treatment Initiative	13	15: placebo

Author	Setting	Cohort Name/Study Design	N	Comparator Group
Oxenius et al[100]	ER	Clinical	8	—
Pantazis et al[101]	ER, NA, AUS	CASCADE	1023	—
Prazuck et al[102]	ER	Clinical	20	18 HIV+ ART naive
Reider et al[68]	ER	Zurich Primary HIV cohort and Swiss HIV Cohort Study	111	—
Rosenberg et al[103]	NA	Clinical	18	6 AHI ART naive
Rosenberg et al[104]	NA	RCT: ACTG A5187 Study	20	—
Saez-Cirion et al[105]	ER	VISCONTI	14	Untreated HIV controllers, viremics, and treated chronics
Seng et al[106]	ER	ANRS PRIMO and SEROCO	293	—
SPARTAC Trial Investigators[107]	Multicountry	RCT: SPARTAC Trial	120: 12 wk ART 118: 48 wk ART	124 standard of care (no ART)
Steingrover et al[108]	ER	Clinical (TRIESTAN study controls)	26	46 HIV+ controls; initiated ART during chronic infection
Steingrover et al[109]	ER	Dutch HIV Monitoring Foundation Cohort/Amsterdam Cohort Studies	32	250 HIV+ late ART initiators
Stekler et al[50]	NA	Seattle Primary Infection Cohort (historical controls)	157	27 historical + 60 contemporary controls
Streeck et al[110]	ER	Clinical	12	8
Tilling et al[111]	ER, AUS	Quest Study	—	—
Vinikoor et al[112]	NA	Open-label treatment trial	31	30 HIV− controls
Volberding et al[113]	NA	ACTG 371 single-arm trial	28	45 “recent” HIV infections (versus acute)
Wyl et al[114]	ER	Zurich Primary HIV cohort (Swiss HIV Cohort Study controls)	33	79 chronic HIV, ART naive
Younes et al[115]	NA	Clinical	39	—

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Ananworanich et al[15]	3 arms of elective ART: 5 class “megaHAART” versus 3 class regimen initiated within 3 d of enrollment for 24 wk	AHI: M	$CD4^+CCR5^+$ gut T cells increased from 41% at baseline to 64% at 24 wk	<50 copies achieved in 14/15 patients in blood and 13/13 in gut. Total blood HIV DNA at 0 wk predicted reservoir size at 24 wk
Archin et al[71]	ART within 45 d of EDI	AHI: B and F	Degree of resting cell infection is directly related to the availability of $CD4^+$ T cells susceptible to HIV, regardless of whether viremia is controlled by the immune response and/or ART	Success of early ART may depend to a certain extent on whether or not infected resting $CD4^+$ T cells are stable
Bacchus et al[72]	ART initiated 10 wk postinfection for 3 yrs	—	—	HIV DNA reservoir distributed large in short-lived memory $CD4^+$ T cells
Cellerai et al[73]	ART initiation within 13 d of seroconversion	SC: (A and B) and/or	Early ART results in levels of highly polyfunctional HIV-1–specific $CD4^+$ and $CD8^+$ T	—

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
		(C and/or F)	cells as in long-term nonprogressors	
Desquilbet et al[74]	17 m	RI: F or [B or (A and B)] or E PHI: G	—	No difference in viral set point 12 mo after treatment discontinuation in the treatment group compared with matched controls
Evering et al[75]	ART started within 72 h of flexible sigmoidoscopy	AHI: M	ART may halt measurable evolution of HIV-1 quasi-species derived from the gastrointestinal tract; meaning immune activation in the gut may persist whether or not there is viral replication	—
Fidler et al[76]	3 arms of elective short course: 4 drug, 3 drug, PI only	AHI: G or F or (A and B) or L	No differences in rate of CD4 recovery by arm	Faster VL decline in patients on 4 drug regimen compared with 3 drug or PI-containing ART
Fidler et al[77]	Elective 3 mth short course at PHI	PHI: E or F or L	Rate of CD4 decline slower in treated group over 3 yrs	No difference in mean VL at 2 yrs
Gay et al[78]	NNRTI-based 3 drug regimen initiated during AHI	AHI: A and B	Relatively high median baseline activation level of $CD8^+CD38^+HLA\text{-}DR^+$ T cells	More rapid viral decline in treated AHI patients than controls
Gianella et al[79]	Elective standard 1st line within 120 d of EDI; option to stop after 1 yr of suppression	AHI: G and [D and (B and/or H)] RI: I or (B and J) and (F or I) or K	—	Early ART associated with lower plasma and cell RNA as compared with late starters and ART naive for >1 yr after ART cessation
Goujard et al[80]	ART = continuous therapy; ART-STI = 36 wk ART with three 4 wk interruptions; ART-STI-IFN = same as ART-STI group with addition of peg-IFN	AHI: B and D PHI: D	$CD4^+$ T-cell counts and $CD4^+/CD8^+$ T cell ratios similar between groups after 6 mth interruption; HIV-specific responses didn't differ across arms. interruption didn't have deleterious impact; all regimens show sustained immunological benefit after cessation	87% of the patients achieved undetectable RNA at 32 wk; but RNA and HIV DNA levels were same after 6 mth interruption
Goujard et al[81]	Standard therapy according to national guidelines within 3 mth of EDI who interrupted and stayed in follow-up ≥ 12 mth	PHI: (B and D) or E	Controllers had lower levels of specific $CD8^+$ T-cell frequency and $CD8^+$ T-cell activation	14/164 patients controlled VL for median 4.5 yrs
Grijsen et al[82]	Forty-five 24 wk SCART; thirty-nine 60 wk SCART; both triple class regimen	PHI: (B and D) or (A and J within 180 days)	—	—
Grijsen et al[83]	3 class regimen for 24 or 60 wk; changed if DR or poor tolerance	PHI: (A and B) or (A and J within 180 d)	Time to reinitiation of therapy longer in both ART arms	ART lowered viral set point (plasma VL at 36 wk after interruption)
Hecht et al[84]	Elective ART for ≥12 wk within 6 mth of seroconversion; subsequently interrupted	EHI/PHI: (A and B) or E or (A and F)	$CD4^+$ T-cell counts higher in early group at 24 and 72 wk	Differences in RNA levels across groups at 24 wk gone by 72 wk

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Hocquelox et al[85]	ART within 3 mo of PHI, interruption after ≥3 mth with/≥24 mth follow-up	PHI: (D and H) and/or E	Controllers had more stable $CD4^+$ counts over time	5/32 controlled VL for med 6.25 yrs
Hoen et al[86]	Randomized to 1/4 regimen types	PHI: (A and B) and G	Median increase in $CD4^+$ 147 cells/mL by 48 wk	Median decrease in VL −5.4 log copies by 48 wk. Baseline $CD8^+$/$CD38^{++}$ T-cell count predictive of suppression
Hogan et al[87]	ART for 36 wk	RI: F or (A and/or D within 180 d)	Trial stopped by DSMB due to higher-than expected disease progression in delayed treatment arm	—
Jain et al[88]	—	AHI/EHI: "within 6 mo of infection"	Delayed ART group had higher levels of $CD4^+$ and $CD8^+$ T-cell activation	Delayed therapy associated with higher proviral and plasma DNA. % of activated $CD4^+$ and $CD8^+$ T cells associated with size of reservoir
Jansen et al[89]	Intensive 5-class regimen initiated "within weeks of EDI"	AHI: D or G	ART associated with more HIV- specific $CD4^+$ T cells but this wasn't associated with ability to control VL post-ART	ART associated with lower VL; 1/5 interrupters controlled VL up to 2 yrs later.
Kaufman et al[90]	Standard 1st line with supervised treatment interruption (STI) protocol	AHI: (A and B) or (C and D) EHI: G or F	Gradual decrease in $CD4^+$ and viremia levels over time after interruption; baseline HIV-specific immune activation did not predict duration of viral control	
Kinloch-de Loes et al and Koegl et al[91,92]	Daily zidovudine	PHI: (G and K) or (H and A and B)	CD4 cell counts differed across arms by 6 mth	—
Koegl et al[92]	3 or 4 class regimen as determined by physician, discontinued at median of 9.5 min	PHI: (A and B) or E	Treated group experienced increase in CD4 count; untreated group CD4 fell. Time to CD4 < 3350 significantly shorter in untreated group	Med VL in ART group lower 6 mth post cessation, difference gone by 12 mth
Lampe et al[93]	3 or 4 class regimen as part of vaccine trial; interruption optional	PHI: (G and K) or (H and A and B)	—	Unsuppressed VL prevalence at 3 yrs higher in untreated, but effect of transient ART on long-term VL is likely modest
Le et al[94]	97 initiated within 4 mth post-EDI; 116 initiated after 4 mth EDI	PHI: K	Earlier ART initiation was associated with larger portion of and faster pace of $CD4^+$ T-cell recovery	No association between VL at ART initiation and $CD4^+$ T-cell recovery
Lodi et al[95]	ART initiated within 3 mth of seroconversion for ≤3 mth	SC: (A and B) and/or E	—	95.8% experienced virological rebound within median 1.7 mth after treatment interruption
Markowitz et al[96]	ART initiated during EHI; voluntarily discontinued after mean 3.2 yrs	RI: B and L	$CD4^+$ and $CD8^+$ cell–mediated HIV-specific immune responses increased	Posttreatment viral rebound present in all subjects after mean 26 d, followed by a significant but transient (mean 1 yr) suppression in all but 1 subject

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
Mehandru et al[97]	ART initiated during acute/ early infection. Range 1–7 yrs of ART	AHI: M	ART during AHI/EHI does not lead to complete immune reconstitution in the GI mucosa despite immune reconstitution in the peripheral blood	—
Moir et al[98]	ART	EHI: "within 6 mth of providing baseline samples"	Early ART associated with better B-cell function recovery against HIV and non-HIV antigens	—
Niu et al[99]	Daily high-dose zidovudine	AHI: (H and A and B) or K	Significantly higher CD4 in treated subjects after 6 mth of therapy	No difference across 2 arms in plasma VL after 6 mth
Oxenius et al[100]	3 class regimen initiated either at seroconversion or 6 mth after	AHI: G and K	ART during PHI preserves HIV-specific $CD4^+$ and $CD8^+$ T cell physically and functionally (HIV-specific immunity), even when ART is intermittent	—
Pantazis et al[101]	Early (N = 675) treated within 6 mth of seroconversion for ≥30 d; deferred (n = 348) treated after 6 mth	AHI: E or (A and B) or L	CD4 cells lost rapidly after cessation but subsequent loss rate equal to untreated	No difference in VL set points, defined as mean of all available VL measures post-ART
Prazuck et al[102]	Elective ART initiated within 10 wk of symptomatic AHI; at least 12 mth before interruption	AHI: (A and B) or (D and H)	Early ART associated with higher CD4 2.8 yr after cessation	25% of treated group controlled RNA 2.8 yr after cessation
Reider et al[68]	93 elected to initiate ART early; approximately 51% stopped after 1-yr suppression	AHI: G and [D and (H and/or B)] RI: G and (B and J) and I	Phylogenetic cluster study to examine transmission dynamics identified 20 clusters; 5 inferred transmissions occurred during chronic stage among presumed transmitters >3 m after cessation.	
Rosenberg et al[103]	3 class regime, most within 72 h of diagnosis with STI if VL exceeded 5000 copies	AHI: A and B and D	Increased HIV-specific T cells and stable T helper cells responses, suggesting a functional immune responses can be augmented in chronic infection	Despite rebound in viremia, all subjects were able to achieve at least a transient steady state off therapy with viral load below 5000 RNA copies per milliliter
Rosenberg et al[104]	ART initiated during acute/ early infection, interrupted at 30 wk; 1:1 randomization of vaccine versus placebo	AHI: B and D	All subjects had "relatively healthy CD4" counts	Med viral set points (defined as average of all measured VL after ART) lower in all subjects as compared with historical controls (MACS)
Saez-Cirion et al[105]	ART initiated within 10 wk of PHI	PHI: D and (H or B) and or E	—	HIV suppressive capacity of $CD4^+$ cells and T-cell activation status lower in posttreatment patients than HIV controllers
Seng et al[106]	ART initiated during PHI for ≥6 m; interrupted for ≥3 m (PRIMO); 35% given monotherpay, rest combo-ART	PHI: D or ((B or H) and B) or E	Rapid CD4 decline in first 5 m after cessation, more slowly thereafter. More rapid gains in CD4 during ART	—

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
			associated with greater loss after cessation	
SPARTAC Trial Investigators[107]	3 class regimen as determined by physician	PHI: E or (A and B) or F or L or (G and J)	Time to $CD4^+$ count <350 was 65 wk longer with 48-wk course versus SOC	48-wk course conferred lower RNA levels 36 wk after cessation versus SOC
Steingrover et al[108]	3 or 4 class regimen, simplified 1 yr after initiation; subsequent interruption	PHI: (D and (B or H)) or E	Significantly greater drop in $CD4^+$ cell count in later initiators within first 4 wk; no difference after 4 wk	Time to viral rebound (50–500–5000 copies) significantly longer in earlier ART initiators
Steingrover et al[109]	3 or more class regimens; early initiation within 180 d with early interruption	PHI: [(A and D) and (B or H)] or E	No significant difference in rate of CD4 decline between 2 groups	Early transient ART associated with a initial but transient lowering of viral set point, defined as 7 wk after seroconversion or 7 wk after ART interruption
Stekler et al[50]	40: ART <30 d; 82: ART 31–180 d; 35: ART >180 d	AHI: A and B EHI: D and F	—	—
Streeck et al[110]	ART for 24 wk during AHI	AHI: G and K and [B and (C or D)]	Treatment associated with increased CD4+ cell count, enhanced differentiation of HIV-specific $CD8^+$ T cells from effector memory to effector cells at week 24, and higher virus-specific interferon-g+ $CD8^+$ T-cell responses after viral rebound at 48 wk. But by 6 m no difference in CD4 count	Treatment resulted in suppression of viremia at 48 wk but no difference at 6 mth after termination
Tilling et al[111]	4 class regimen during PHI	PHI: B and [A and/or (C and D)]	Rapid decline and normalization of $CD8^+$/$CD38^{++}$ cell counts within 2 wk of ART and continued to fall in suppressed patients	80% suppressed on therapy, most of whom (67%) continued to have falling $CD8^+$/$CD38^{++}$ cell counts
Vinikoor et al[112]	ART initiation within 45 d of AHI diagnosis; for those suppressed for 96 wk	AHI: A and B	% of $CD8^+$ cells with $CD38^{++}$HLA- DR^+ decreased from 72.6% to 15.6% in 96 wk but was higher than HIV− controls	Shorter time to suppression predicted lower activation at 96 wk
Volberding et al[113]	4 class regimen in acute or recent HIV with interruption after 52 wk of suppression until viral rebound	AHI: B and [A or (C and D)] or (D and E) RI: ((C and D) and (A and B)) or (C and F)	Baseline percentages of activated $CD8^+$ T cells, naive and memory CD4þ and CD8þ T cells, and absolute CD4þ and CD8þ T-cell counts were not associated with primary end point success	End point of viral suppression for 24 wk postinterruption achieved at same rate in both arms
Wyl et al[114]	Elective std 1st line; option to stop after 1 yr of suppression	AHI: E and [C and (G and/or B)] RI: E and (B and I) and H	—	VL (both plasma and cell associated) lower in treated versus untreated controls 1 yr after ART cessation, but no difference by 3 yrs
Younes et al[115]	1 yr of ART initiated at 5 different time points up to 18 mth postseroconversion	SC: (A and B) or G or D or F and K	Earlier ART inhibits generation of significant frequencies of HIV-specific Tm cells. Later ART limits HIV-specific CD4 T-cell responses. ART initiation between 3–18 m show brisk	—

Author	Treatment	Definition of SC, EHI, PHI, AHI, and RI	Immunological Outcomes	Virological Outcomes
			and broad HIV-specific CD4 T-cell responses	

A, enzyme immunoassay (EIA) negative; AUS, Australia; AHI, acute HIV infection; B, detectable plasma HIV RNA; C, EIA positive; D, Western blot negative or indeterminate; E, negative and positive EIA result within 12 months; ER, Europe; F, detuned nonreactive EIA; G, acute retroviral syndrome symptoms, most commonly including fever, malaise, headache, lethargy, and malaise; H, detectable p24 antigen; I, negative gp120 avidity; J, Western Blot positive; K, duration from estimated date of infection based on at least one of the following (1) onset of ARS symptoms, (2) a documented high-risk exposure, or (3) estimated date of infection determined by laboratory methods; L, evolving titer-positive HIV antibody test; M, Fiebig acute HIV staging (<30 days postinfection); NA, North America; PHI, primary HIV infection; RI, recent infection; SC, seroconversion.