REVIEW PAPER

Current clinical trials update on HIV/AIDS: a systematic review

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Abstract

Several clinical trials using different interventions are being sponsored to combat human immunodeficiency virus (HIV) at different stages. For evidence-based knowledge studies in medicine, clinical trials are of utmost importance. A legislative requirement to register the clinical trials at the ClinicalTrials.gov provides the information necessary for intensive evaluation, which was previously not possible. The purpose of this study was to provide an intensive portfolio of HIV clinical trials and perform a retrospective ClinicalTrials.gov data review. All active, open, and recruiting clinical trials registered at ClinicalTrials.gov up to May 2018 were included. Information related to trial characteristics, intervention type, primary outcome, and patient enrollment timeline was extracted. Information related to 10,182 registered HIV trials was download from ClinicalTrials.gov. Phase 2 clinical trials were the major ones comprising nearly 1.6% of total clinical trials with the industry being the major sponsor followed by NIH. Other characteristics analyzed included the number of trial centers, primary outcome, treatment setting, and time relation with phases. Common intervention were classified into adjuvant, non-adjuvant, and radiotherapy. The clinical trials data analysis provides a comprehensive description of HIV trials. The information provided may be useful to re-tailor the intervention techniques and to overcome the discrepancy in data management for clinical trials which would improve clinical trial design, and reduce failures and cost of trials.

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Key words: clinical trials, HIV, AIDS, ClinicalTrials.gov, data interpretation.

Introduction

Zoonotic infections with simian immunodeficiency viruses from African primates led to the human immunodeficiency virus (HIV) epidemic. The first group to be infected with HIV were bushmeat hunters. Apes and sooty mangabey monkeys were the source of transmission for HIV-1 and HIV-2 respectively [1]. There are several factors that increase risk of sexual transmission of HIV-1. The major one is the number of copies per ml of plasma HIV-1 RNA (viral load). With every 1 log10 increase there is 2.4 times increased risk of sexual transmission [2]. Other factors include pregnancy [3], sexually transmitted infections (herpes simplex type 2 infection [4], genital ulcers [5], and bacterial vaginosis [6]), and receptive anal intercourse [7]. Multiple sexual partners [8] and concurrent partnerships [9] are among the behavioral factors associated with increased HIV-1 sexual transmission, whereas male circumcision is associated with a reduced risk of sexual transmission of HIV [10].

HIV continues to be a major global public health issue, with nearly 78 million people infected since the start of the epidemic. Moreover, an estimated 35 million people have died of AIDS-related illnesses. 1,122,900 adults and

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adolescents were living with HIV at the end of 2015, and 162,500 (15%) of those had not received a diagnosis. Among people aged 13-24 who were living with HIV, around 44% did not know about their infection. In 2016, 18,160 people received an AIDS diagnosis and since the epidemic began in the early 1980s, 1,232,346 people have received an AIDS diagnosis. Gay and bisexual men have accounted for 67% (26,570) of all HIV diagnoses and 83% of diagnoses among males. Black/African American and bisexual men accounted for the largest number of HIV diagnoses (10,223), followed by Hispanic/Latino (7,425) and white (7,390) gay and bisexual men. From 2011 to 2015, diagnoses decreased by 10% amongst white gay and bisexual men. Among Hispanic/Latino gay and bisexual men, diagnoses increased by 14%. Heterosexual contact (injecting drugs) accounted for 24% (9,578) of HIV diagnoses. Women accounted for 19% (7,529) of HIV diagnoses [11, 12].

The Centers for Disease Control and Prevention (CDC) uses data from the National HIV Surveillance System and the Medical Monitoring Project to estimate the percentages of persons living with HIV infection and treated with antiretroviral drugs (ART). According to 2011 data, an estimated 40% of HIV diagnosed patients were engaged in HIV medical care, 37% were prescribed ART, and 30% achieved viral suppression. The effect of ART therapy and viral suspension varied among different age groups with persons aged ≥ 65 years showing the highest viral suspension (37%) compared to 18-24 years (13%), 25-34 years (23%), and 35-44 years (27%) age group patients [13]. Improved health, prolonged lives, and prevention of transmission are benefits associated with ART. Future research work is focused on developing therapeutic strategies to induce sustained ART-free remission by employing an approach known as analytical treatment interruption [14].

Funding is another issue associated with HIV and AIDS. In recent years, a plateauing of global funding towards HIV and AIDS has been seen, with US$ 19 billion invested among low- and middle-income countries [12]. From 2006 to 2016 domestic investment (increasing on average of 11%) by several countries has pushed to overcome the insufficient international funding issue. Future commitment suggestions to overcome the HIV and AIDS epidemic have been estimated by the United Nations General Assembly at US$ 23.9 billion in 2020 and with US$ 23.9 billion required in 2030 [12].

We provide a global overview of the clinical trial statistics in HIV/AIDS infection. We briefly describe different characteristics for trial design and type of interventional studies used for HIV/AIDS infection. Finally, we provide a time-line of patient enrollment and registered patents for lung cancer and discuss the advantages, challenges, and perspectives for the improvement of clinical trial design for HIV/AIDS studies.

Material and methods

Data source

On March 1, 2018, a data set of 10,182 clinical studies related to HIV/AIDS was downloaded from ClinicalTrials.gov. The dataset was analyzed using various parameters in Excel. Information regarding terminologies can be obtained from the Clinical Trials Transformation Initiative website [15].

Study design and parameters

The data were restricted to active recruiting studies. In the advanced search option the following parameters were selected: "open/recruiting/active studies for recruitment sta-

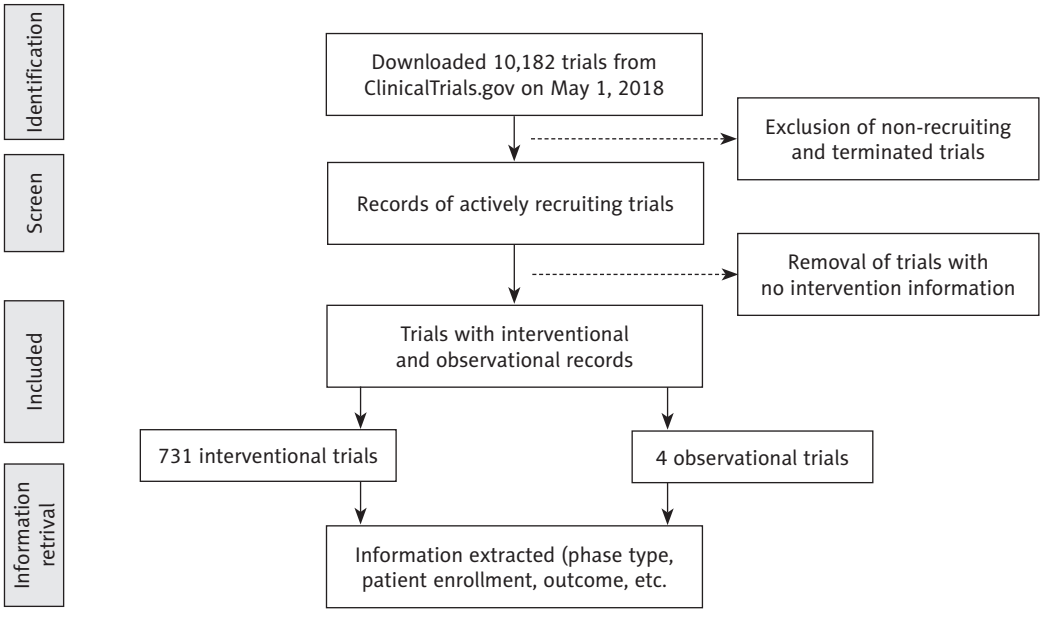

Figure 1. Flowchart of study selection

tus", "all groups" for study, and age groups. The data extracted comprised both interventional and observational studies. We wanted to keep this review current, so we excluded all completed/terminated/not recruiting clinical trials from our search. Further clinical trials with no intervention information were excluded. The information contains all active clinical trials on HIV/AIDS until May 2018 in the ClinicalTrials.gov database. Each study was manually reviewed by the authors (title, interventions, outcome measures, recruiting status, MeSH terms, and the full ClinicalTrials.gov record if necessary) to ascertain relevance to HIV/AIDS study. Figure 1 depicts the workflow selected for final data extraction for analysis.

Data collection and analysis

The following information was extracted from the website: (1) clinical trial phase (early phase 1, 1/2, 2, 2/3, 3, 4) (2) recruiting status, (3) location of clinical center, (4) study design, (5) type of study (interventional, observational or others), (6) number of trial centers, (7) primary sponsor, (8) primary outcome, (9) treatment setting, (10) treatment classes, (11) time relation with phases. Along with that we also compiled information about patents related to HIV/AIDS using HIV/AIDS treatment, HIV/AIDS therapeutic, and HIV/AIDS diagnostic. The information extracted was: (1) number of patents published, (2) patent office location, (3) primary applicant name, and (4) biologicals.

Results

Trial characteristics and design

Our parameters identified 10,182 trials involving HIV/AIDS. 1161 had no treatment information or missing information regarding a location of clinical trials and were excluded from the total clinical trials identified. Overall, 382 (3.7%) were actively recruiting, 110 (1.08%) were not yet recruiting, and 19 (0.1%) were enrolling by invitation only. For 323 trials (3.1%) no information regarding the recruiting status was available, but we included them in our data analysis studies as these clinical trials showed up in our advanced search option when we selected for open and active studies. The characteristic numbers of these phases were as follows: Phase 1 trials (159, 1.5%), Phase 1/2 (56, 0.5%), Phase 2 (168, 1.6%), Phase 2/3 (35, 0.3%), Phase 3 (170, 1.6%), and Phase 4 (149, 1.4%). The major sponsor for clinical trials was the NIH, accounting for 2.2% of trials. More than half of total clinical trials 794 (7.7%) were conducted in the US, whereas those outside the US comprised the remaining 902 (8.2%) clinical trials. A major portion of trials were interventional type, 731 (7.1%), indicative of proper treatment/drug provided to one or more group to test for its effects. Moreover, as clinical trials are committing in cost, workload, and recruitment, more than half of the clinical trials were conducted at multiple locations (Table 1). A major proportion of the phase 2 (phase 1

Table 1. All open clinical trials characteristics. Data generated from ClinicalTrials.gov

Factor	No. of trials (%) Total: 10,182
Type of clinical trials	
Phase 1	159 (1.5)
Phase 1/2	56 (0.5)
Phase 2	168 (1.6)
Phase 2/3	35 (0.3)
Phase 3	170 (1.6)
Phase 4	149 (1.4)
Unspecified	1161 (11)
Primary sponsor	
Industry	232 (2.2)
NIH	188 (1.8)
Thai Red Cross AIDS Research Centre	1 (0.009)
Royal Thai Army Clinical Research Center	1 (0.009)
AFRIMS	1 (0.009)
Bang Lamung District Hospital	1 (0.009)
Emory University	1 (0.009)
Botswana Ministry of Health clinics	1 (0.009)
Brooke Army Medical Center	1 (0.009)
VA Portland Health Care System	1 (0.009)
Dallas VA Medical Center	1 (0.009)
Infectious Diseases Institute	1 (0.009)
Naval Medical Center San Diego	1 (0.009)
Chulalongkorn University Hospital	2 (0.01)
Eastern Virginia Medical School	1 (0.009)
Others	344 (3.3)
Recruiting status	
Actively recruiting	382 (3.7)
Not yet recruiting	110 (1.08)
Active, not recruiting	224 (2.1)
Enrolling by invitation	19 (0.1)
Unknown	323 (3.1)
Study locations	
Single	1114 (10.9)
Multiple	582 (5.71)
Unspecified	203 (1.99)
Location of trial centers	
Within US	794 (7.7)
Outside US	902 (8.8)
Type of study	
Interventional	731 (7.1)
Observational	4 (0.03)
Others	0 (0)

Table 2. Characteristics of phase II and III clinical trials

Study design	No. of phase I trials (%)	No. of phase II trials (%)	No. of phase III trials (%)	No. of phase IV trials (%)
Randomization				
Randomized	162 (1.5)	127 (1.2)	130 (1.2)	101 (0.99)
Non-randomized trials	41 (0.4)	21 (0.2)	11 (0.1)	14 (0.13)
Open label	24 (0.2)	22 (0.2)	20 (0.1)	8 (0.07)
Single-blinded	100 (0.9)	75 (0.7)	47 (0.4)	49 (0.4)
Double-blinded	19 (0.1)	19 (0.1)	26 (0.2)	4 (0.03)
Number of treatment arms				
Single arm	1 (0.009)	0 (0)	0 (0)	0 (0)
Two arms	0 (0)	0 (0)	0 (0)	0 (0)
Three or more	0 (0)	1 (0.009)	0 (0)	0 (0)
Type of control arm				
Placebo	55 (0.5)	51 (0.5)	34 (0.33)	13 (0.1)
Standard care or active control	0 (0)	0 (0)	0 (0)	1 (0.009)
Primary outcome				
Overall survival	10 (0.09)	20 (0.1)	9 (0.08)	0 (0)
Progression-free survival	3 (0.02)	4 (0.03)	1 (0.009)	0 (0)
Quality of life	3 (0.02)	11 (0.1)	24 (0.2)	13 (0.1)
Disease-free survival	0 (0)	6 (0.05)	2 (0.01)	0 (0)

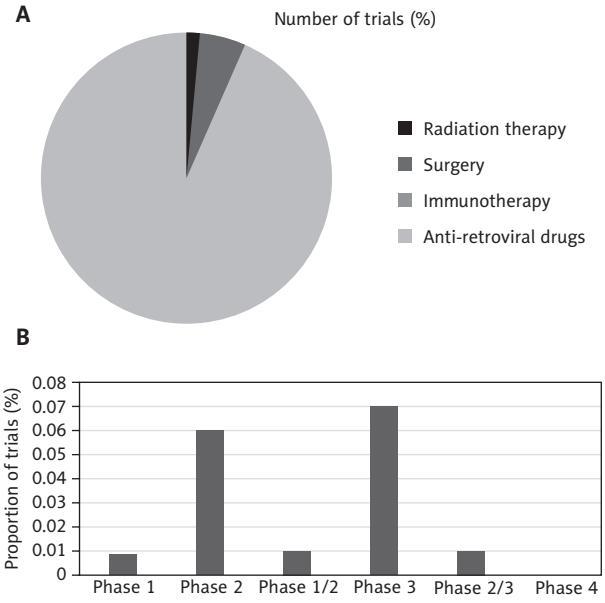

Figure 2. Types of treatment for HIV in clinical trials phase I-IV. **A)** Types therapy for treating HIV. **B)** Biomarker analysis studies in clinical trials

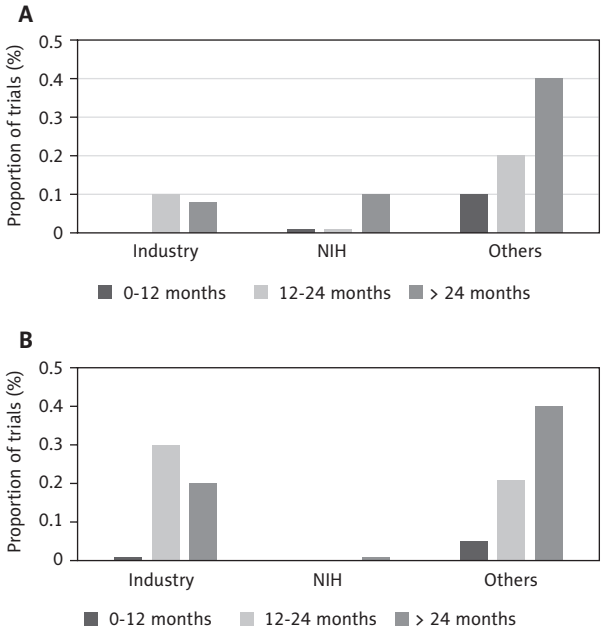

Figure 3. Clinical trials time line for patient enrollment. **A)** Phase II and **B)** phase III

+ phase 1/2) trials were randomized (1.5%) or single-blinded (0.9%). For phase 1 and phase 2 (0.009%) the standard care or active control was the major arm (Table 2). Overall survival was the major primary outcome in all phases of trials (phase 1, 0.09%; phase 2, 0.1%; phase 3, 0.08%) followed by progression-free survival (phase 1, 0.02%; phase 2, 0.03%; phase 3, 0.009%), and quality of life (phase 1, 0.02%; phase 2, 0.05%; and phase 3, 0.01%) (Table 2).

Intervention type and treatment settings

HIV/AIDS treatment involves several types of therapeutic methods as seen in Figure 2. Adjuvant therapy was the most used intervention for nearly 0.06% of clinical trials. This was followed by non-adjuvant therapy (0.03%) followed by second line and radiotherapy comprising 0.02% and 0.01% clinical trials respectively (Table 3 and Table 4, Figure 2A).

Biomarker analysis

Early detection of HIV/AIDS plays a key role in successful treatment. Recently, several research studies have focused on identifying and detecting specific biomarkers in HIV/AIDS. We also analyzed data from all phases and found out that for 36 clinical trials as a study objective a biomarker was included. In clinical trials biomarker information was provided for (Figure 2B) Phase 1 (1, 0.009%), Phase 2 (7, 0.06%), Phase 1/2 (2, 0.01%), Phase 3 (8, 0.07%), and Phase 2/3 (2, 0.01%)

Patient enrollment timeline

Patient enrollment in Phase 2 and Phase 3 clinical trials were also taken into consideration. The success of results generation of a clinical trial depends on statistical analysis of the number and time of patient enrollments. Industry-sponsored Phase 2 clinical trial were open for more than 2 years (0.08%) and were of smaller proportion compared to NIH sponsored clinical trials. Phase 3 clinical trials had a similar trend with the NIH-sponsored trial taking the lead along with nearly 0.1% compared to industry-sponsored clinical trials. Again, patient enrollment was not provided for a large number of NIH sponsored Phase 3 clinical trials (Figure 3).

Table 3. Chemotherapy treatment settings and biomarkers for clinical trials

Treatment setting	No. of trials (%)
Adjuvant therapy	7 (0.06)
Neoadjuvant therapy	4 (0.03)
Adjuvant/neoadjuvant therapy	0 (0)
Radiotherapy	2 (0.01)
Advanced-stage disease	
First line	2 (0.01)
First or second line	0 (0)
Second line	3 (0.02)
Maintenance	8 (0.07)
Biomarker(s) specified	
Yes	36 (0.3)
Phase of trial	
Phase 1	1 (0.009)
Phase 2	7 (0.06)
Phase 1/2	2 (0.01)
Phase 3	8 (0.07)
Phase 2/3	2 (0.01)
Phase 4	0 (0)

Table 4. Types of treatment for HIV in clinical trials

Treatment	Number of trials (%)
Radiation therapy	9 (0.08)
Surgery	31 (0.3)
Immunotherapy	3 (0.02)
Anti-retroviral drugs	590 (5.7)

Discussion

Our contemporary survey provides a landscape of registered HIV/AIDS clinical trials including interventional and observational studies. Various characteristics of trials such as design, location, type of intervention, patient enrolment, and sponsors are discussed. Several noteworthy observations emerge from this review of clinical trials of HIV/AIDS. The survey suggested the majority of trials on the ClinicalTrials.gov website were phase 2. As setting up clinical trials requires intensive utilization of resources, money, and patient enrolment, HIV/AIDS trials were majority multi-centered and were sponsored by industry, NIH, and universities. In our analysis, several data points were unspecified as the trial lacked the information for that specific column. NIH phase 2 clinical trials were open for a longer time compared to industry-sponsored trials.

One of the major problems with all these clinical trials was the absence of biomarkers in phase 2 trials, and a similar pattern is followed at phase 3 lung cancer trials. For only 0.3% of total clinical trials biomarker analysis information was available. For future success, early-stage clinical trials aiming at the better understanding of pathways and molecular level studies need to be implemented before moving forward with large clinical trials. Moreover, biomarker analysis collection needs to be an active step in future development. Enrolling more patients for early-stage HIV/AIDS would be a good way to overcome this limitation. The biomarker selection for molecularly targeted therapy and development of novel therapy/biomarker using studies performed on tissue samples could dramatically improve the cure rates in HIV/AIDS. Other important factors to consider when designing clinical trials are mainly related to the complex and difficult ethical challenges. These mainly include scientific validity for clinical trials, fairness in the selection of study sites and participants, consideration of risk/benefit ratio, independent ethical and scientific review, and informed consent [16, 17].

Conclusions

Based on the data collected from ClinicalTrials.gov, our analysis reveals that the majority of clinical trials were phase 2, with NIH trials lasting for more than 2 years of enrollment and radiation, surgery and chemotherapy being the major interventions. Most of them were randomized trials with the primary outcome focused on patient survival. Moreover, if successful interventions related to HIV are found in clinical trials then efforts should be made to direct funding towards patients from low economy countries. Our comprehensive analysis provides useful information regarding HIV/AIDS which may be helpful to industry and investigators for future decisions.

Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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